

1 A Reappraisal: Natural History of Amniote Reproductive Modes In Light of Comparative  
2 Evolutionary Genomics

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7 **Abstract**

8

9       There is a current lack of consensus on the ancestral parity mode, oviparity (egg-laying) and  
10 viviparity (live-birth), of amniotes and squamates (snakes and lizards). How transitions between  
11 parity modes occur at the genomic level has primary importance on how science conceptualizes  
12 the origin of amniotes, and highly variable parity modes in Squamata. Within the context of  
13 interdisciplinary literature—medical, poultry science, reproductive biology, and evolutionary  
14 biology—I review the genomics and physiology of five broad processes expected to change  
15 during transitions between parity modes: eggshell formation, embryonic retention, placentation,  
16 calcium transport, and maternal-fetal immune dynamics. Throughout, I offer alternative  
17 perspectives and testable hypotheses regarding proximate causes of parity mode evolution in  
18 amniotes and squamates. Should viviparity have evolved early in the history of Lepidosauria, I  
19 offer the basal cap hypothesis as a proximate explanation. The framework of this hypothesis can  
20 be extended to amniotes to infer their ancestral state. I also provide a mechanism through which  
21 squamates may reverse back to oviparity with no intermediate stages. Furthermore, I  
22 contextualize the maternal-fetal immune dynamics in light of modern medical understanding that  
23 embryos are not analogous to allografts (e.g., organ transplants). Overall, this review grounds  
24 itself in the historical literature while offering a modern perspective on a subject that has  
25 fascinated scientists for centuries—the origin of amniotes. I encourage the scientific community  
26 to utilize this as a resource in comparative genomics studies, embrace the complexity of the  
27 system, and challenge new hypotheses proposed.

28

29 *Key Words:* reproductive mode, parity modes, oviparity, squamates, eggshell deposition,  
30 embryonic retention, embryonic calcium transport, maternal-fetal interface, comparative  
31 evolutionary physiology.

32

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90 **I. Introduction**

91

92 A reappraisal is needed for the conceptual framework used to research the evolution of  
93 oviparity (egg-laying) and viviparity (live-birth) in amniotes (birds, non-avian reptiles, and  
94 mammals). Squamates (snakes and lizards) are unique amongst amniotes because they have  
95 highly variable parity modes (Figure 1). Beginning with the first phylogenetic analyses on the  
96 subject, a warm-blooded scientific disagreement has persisted over the labile nature of  
97 evolutionary transitions between parity modes (Blackburn, 1999, 2015; de Fraipont, Clobert &  
98 Barbault, 1996; Griffith et al., 2015; Harrington & Reeder, 2017; Lee & Shine, 1998; Pyron,  
99 2015; Pyron & Burbrink, 2014; Recknagel et al., 2018, 2021b). A growing number of  
100 transcriptomic and genomic studies analyzing the molecular underpinnings of reproductive mode  
101 evolution in squamates (e. g., Brandley et al. 2012; Cornetti et al. 2018; Gao et al. 2019; Griffith et al.  
102 2016, 2017; Foster et al. 2020, 2022; Recknagel et al. 2021a; Yurchenko et al. 2020; Xie et al. 2022) and  
103 recent advances on the ancestral state of amniotes and dinosaurs contribute to this discussion (Jiang et  
104 al., 2023; Norell et al., 2020). It is prudent to acknowledge that the relative difficulty of changing  
105 phenotypes cannot be determined from morphology alone or unidentified physiological  
106 mechanisms. At least theoretically, any phenotypic change could be facilitated by simple  
107 genomic changes (e.g., a single nucleotide polymorphism) or any combination of multi-omic  
108 changes to any number of loci. As research begins to reveal the molecular networks involved  
109 with parity mode evolution, it is important to avoid bias that could be introduced by assumptions  
110 on the feasibility of transitions. Through synthesis of modern and historical research on amniote  
111 reproduction, this review aims to provide greater context for hypotheses testing ancestral states  
112 of parity modes in amniotes and squamates.

113           The earliest estimates predicted that viviparity evolved independently between 90-100  
114 times in squamates (Blackburn, 1982, 1985, 1992). These estimates assumed that oviparity was  
115 the ancestral state and, based on the theoretical grounds of Dollo's law, that reversals back to  
116 oviparity should be exceedingly rare (Blackburn, 1992; Fitch, 1970; Neill, 1964; Tinkle &  
117 Gibbons, 1977). An intermediate phenotype of re-evolving an eggshell has been considered as  
118 physiologically unviable, preventing reversals (Blackburn, 1995; Griffith et al., 2015). This was  
119 demonstrated when experimentally induced extended egg retention in phrynosomatid lizards  
120 resulted in adverse embryonic development attributed to impeded gas exchange imposed by the  
121 eggshell (Mathies & Andrews, 1999, 2000; Parker & Andrews, 2006). However, this result may  
122 be clade-specific.

123           Intermediate phenotypes as fitness valleys assumes 1) eggshells inherently impede gas-  
124 exchange and 2) that an eggshell must re-evolve before a reversal back to oviparity is possible  
125 (Griffith et al., 2015). Contrarily, eggshells are considered a component of the placenta in  
126 viviparous Rough Earth Snakes, *Haldea striatula*, and in viviparous reproductively bimodal  
127 European Common Lizards, *Zootoca vivipara* and Yellow-bellied Three-toed Skinks, *Saiphos*  
128 *equalis* (Stewart, 2013). Additionally, *Saiphos equalis* is a reproductively bimodal skink that has  
129 an oviparous population with incubation times as short as 5 days, thus embryos spend significant  
130 time in utero with an eggshell (Smith et al., 2001). Another surprising example of eggshells  
131 being compatible with full embryonic development includes a report of a captive tortoise that  
132 retained viable eggs until the hatching stage (Kuchling & Hofmeyr, 2022).

133           Several studies predict early origins of viviparity in squamates (Jiang et al., 2023; Pyron  
134 & Burbrink, 2014) and reversals back to oviparity (de Fraipont et al., 1996; Fenwick et al., 2011;  
135 Harrington & Reeder, 2017; Lee & Shine, 1998; Pyron & Burbrink; Recknagel et al., 2018).



136 *Saiphos equalis* proved the possibility of reversals when a viviparous individual oviposited an  
137 egg prior to birthing fully developed young within the same litter (Laird et al., 2019). The  
138 unusual absence of an egg-tooth in oviparous Arabian Sand Boas, *Eryx jayakari* (Lynch &  
139 Wagner, 2010; Staub & Emberton, 2002) serves as additional biological evidence of a reversal,  
140 though this has been challenged (Griffith et al., 2015). Importantly, extended embryonic  
141 retention, characteristic of oviparous squamates compared to birds, is viewed as compatible with  
142 labile transitions (Jiang et al., 2023). Current expectations are that oviparity may re-evolve more  
143 easily in squamate lineages that recently evolved viviparity and which have not lost specific  
144 avian eggshell-matrix proteins (Laird et al., 2019; Xie et al., 2022).

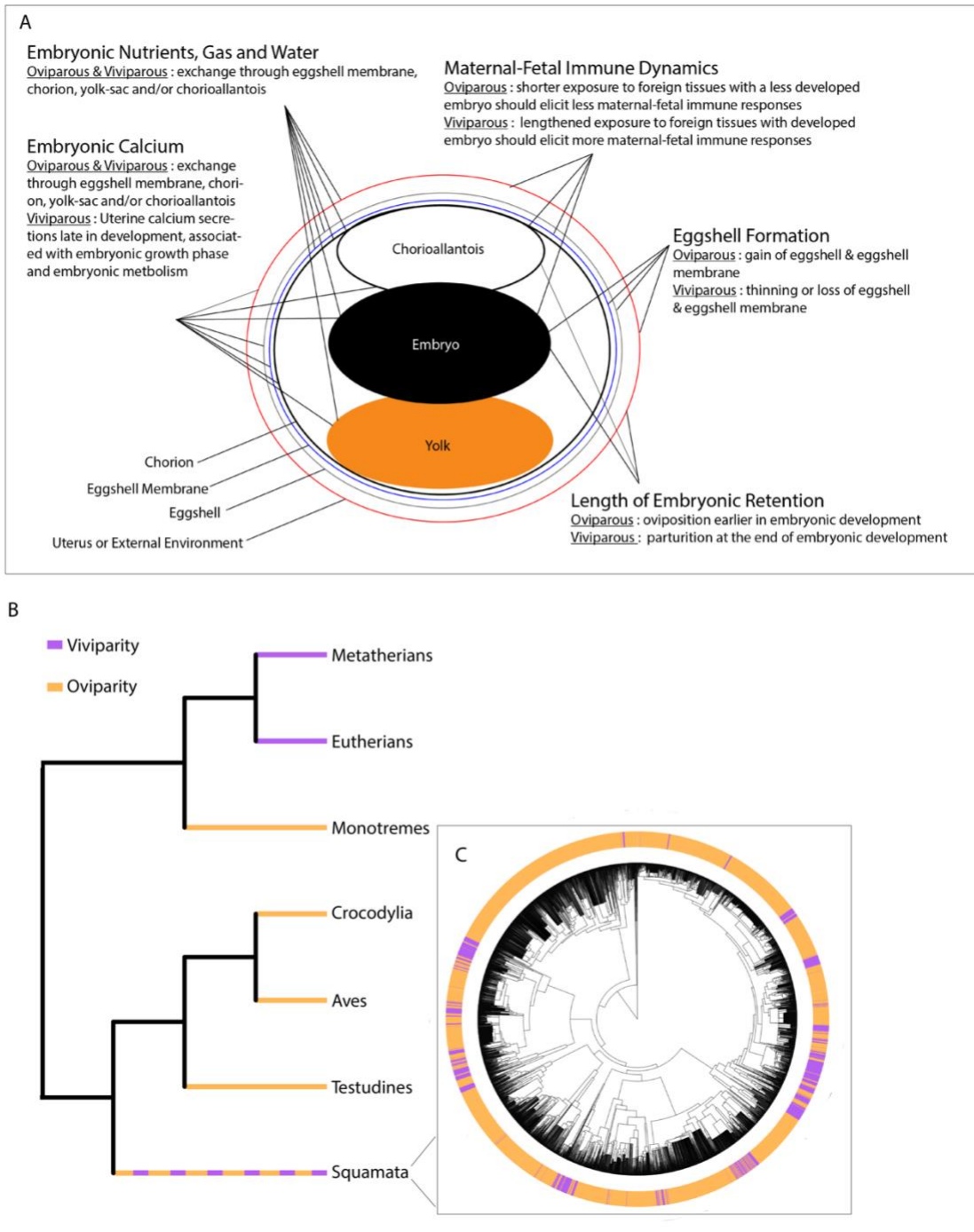
145 Discoveries of viviparity in ancient amniotes are numerous, dating back to the Early  
146 Permian (Chuliver, Scanferla & Smith, 2022; Motani et al., 2014; Piñeiro et al., 2012; Jian et al.,  
147 2023). A viviparous most recent common ancestor of amniotes is not unreasonable. Most  
148 compelling is the report that *Ikechosaurus sp.*, a basal archosauromorph, reached an articulated  
149 stage of embryonic development inside of a parchment shelled egg (Jiang et al., 2023). This  
150 brings support to the extended embryonic retention model (EER) (Hubrecht, 1910). The EER  
151 model postulates that amniote fetal membranes arose through pressure to support exposure to  
152 maternal-fetal tissues during extended embryonic retention (see Laurin et al., 2005 for a  
153 summary of earlier ancestral reconstructions of EER). It serves as an alternative to the widely  
154 accepted model that eggs laid on land prompted the evolution of fetal membranes to retain water  
155 with an eggshell that facilitated gas exchange (Romer, 1957). The discovery that hard-shelled  
156 eggs most likely evolved three times in dinosaurs, deriving from a soft-shelled ancestor (Norell  
157 et al., 2020) is consistent with the EER. As Romer (1957) phrased it “It was the egg which came  
158 ashore first; the adult followed”. This is also consistent with EER, which is compatible with both

159 oviparity and viviparity (Laurin, 2005; Mossman 1987). Throughout this review, considering  
160 viviparity as the most extreme form of extended embryonic retention, I hope to persuade readers  
161 to consider the EER model in a new light. I lay this out through testable hypotheses on the  
162 ancestral eggshell of amniotes and Lepidosaurians (section III.3), a phylogenetic framework to infer  
163 ancestral states based on mechanisms of maternal-embryonic calcium provisioning (section V.2),  
164 and various discussions on what evolutionary comparative genomics reveals about amniote  
165 reproductive mode evolution.

166         Regardless of disagreements, it is sensible to equate the EER with pre-adaptations of the  
167 egg to land. Without substantial amounts of water, converting yolk nutrients to somatic tissue is  
168 impossible (Thompson & Speake, 2003). Water is the primary resource provisioned by the  
169 mother of viviparous squamates and it is stored in extraembryonic membranes (Lourdais et al.,  
170 2015). For example, water and gas exchange are associated with poor chorioallantoic blood flow  
171 (Wootton et al., 1977). In oviparous *Saiphos equalis*, a species with extended embryonic  
172 retention, the chorioallantois thickens to support embryonic growth in late development (Parker  
173 et al., 2010). Thus, if the amniote egg evolved via the EER model, it may have prompted the  
174 origin of extraembryonic membranes of amniotes. This translates to an egg washed ashore that  
175 has already evolved to withstand dryer environments.

176         Although models that restrict parity mode evolution to be unidirectional (from oviparity  
177 to viviparity) are shown to be poor fits for squamates (Pyron & Burbrink; Recknagel et al.,  
178 2021b), there is resistance to the proposition that viviparity originated early in Squamata (e.g.  
179 Griffith et al., 2015). The most recent ancestral state reconstruction, built from biomineralization  
180 and parity mode data across 80 extinct and extant amniotes using a single structured Markov  
181 model, inferred viviparity with extended embryonic retention in the first amniotes and in the

182 most recent common ancestor of Lepidosauria (squamates and sphenodontia) (Jiang et al., 2023).  
183 However, maximum parsimony, and alternative maximum likelihood and Bayesian  
184 reconstructions did not estimate viviparity in the most recent common ancestor of Lepidosauria  
185 (Jiang et al., 2023). A testable hypothesis regarding a molecular mechanism that may have  
186 supported a transition to viviparity at the base of squamates and extended embryonic retention at  
187 the base of amniotes will help conclude these decades long debates.



188

189 **Figure 1:** Schematic demonstrating (A) the anticipated processes that change during transitions  
 190 between oviparity and viviparity, and the organs associated with those changes. Lines from the  
 191 process to different organs indicate the organs expected to be involved with the evolutionary  
 192 shift between oviparous and viviparous phenotypes. (B) relationships between major amniote

193 clades and their associated reproductive mode, and (C) the variation of reproductive modes  
194 across squamates. The squamate phylogeny is adapted from Pyron et al., (2016) and reproductive  
195 modes of squamate species from Pyron & Burbrink (2014).

196

197         The ecological drivers of parity mode evolution are beyond the scope of this review.  
198 However, it is generally proposed that viviparity increases protection from adverse  
199 environmental conditions (Ma et al., 2018; Pincheira-Donoso et al., 2017), and a general trend  
200 that supports this is the higher frequency of viviparous squamates, relative to oviparous,  
201 observed at increasing distances from the equator. The cold-climate hypothesis suggests that  
202 viviparity is an adaptation to cold climates, and this is generally accepted by the scientific  
203 community (e.g. Ma et al., 2018; Zimin et al., 2022). Consistent with the cold-climate  
204 hypothesis, a recent study that utilized 65 million years of global paleoclimate data, squamate  
205 phylogeny and parity data for over 3,000 taxa showed that persistent, stable cold climates are  
206 correlated with transitions to viviparity (Recknagel et al., 2021b). Less focus has been on the  
207 adaptive nature of oviparity. Compared to viviparity, oviparity is associated with higher  
208 fecundity and lessened maternal investment (Recknagel et al., 2019).

209         With a deep review of interdisciplinary literature across amniotes and associated  
210 supplementary materials, I explore genomic and physiological features of gestation and  
211 gravidity, including those that could be exploited to support labile shifts, ancestral viviparous  
212 states in amniotes and squamates, and those that may facilitate or impede reversals. Potentially of  
213 most interest, I propose the framework of the basal cap hypothesis to help elucidate the ancestral  
214 parity modes of squamates and amniotes (section III.3). It details how squamates may have  
215 transitioned to viviparity (an extreme form of extended embryonic retention) early in their

216 evolutionary history. After much consideration, I advocate for using squamates as a model to  
217 understand the ancestral state of the amniote egg. Future work should consider this thoughtfully  
218 and embrace the complexity of the system. I hope this manuscript serves as a foundation for  
219 further research on the evolutionary history of the amniote egg and reproductive mode evolution.

220

### 221 *(1) Terminology*

222 I use the conventional definition of viviparity as retention of eggs until the stage when the  
223 embryo is fully developed (Blackburn & Stewart, 2021; van Dyke et al., 2014). Oviparity is  
224 defined by eggs that develop outside the mother. I use the terms gravidity and gestation to  
225 describe the period of internal retention of the embryo in oviparous and viviparous taxa,  
226 respectively. Vertebrate placentas are conventionally defined by apposition of maternal and fetal  
227 tissues. It is accepted that all viviparous squamates have a chorioallantoic placenta under this  
228 definition (Blackburn & Stewart, 2021; Stewart & Blackburn, 1988). The avian chorioallantoic  
229 membrane and mammalian chorioallantoic placenta are homologous (Metcalf & Stock, 1993). I  
230 sometimes refer to this organ as the chorioallantoic tissue to describe it for both parity modes.  
231 Oviposition refers to the process and act of egg-laying, while parturition refers to the process and  
232 act of giving birth to live-young. Parition refers to both oviposition and parturition (Blackburn,  
233 1992; Smith, 1975).

234

### 235 *(1) Main five physiological changes of parity mode transitions*

236 Several physiological features are expected to change during transitions between  
237 oviparity and viviparity (Figure 1). I break this down into five physiological features (hereafter  
238 Main Five)—1) length of embryonic retention (Murphy & Thompson, 2011; Packard et al.,

239 1977)—only viviparous mothers retain the embryo for the entirety of development; 2) eggshell  
240 formation (Heulin et al., 2005; Packard et al., 1977; van Dyke et al., 2014)—viviparous embryos  
241 generally do not have an eggshell; 3) placental development for maternal-fetal exchange of  
242 required water, gas and/or nutrients (Blackburn, 1992, 2015; Thompson et al., 2000; Thompson  
243 & Speake, 2006); 4) embryonic calcium provisioning (Packard et al., 1985; Shadrix et al., 1994;  
244 Thompson & Speake, 2006)—sources of embryonic calcium and timing of uterine calcium  
245 secretions generally differs between oviparous and viviparous reproduction; 5) maternal-fetal  
246 immune dynamics (e.g., Graham et al., 2011; Hendrawan et al., 2017; Foster et al., 2020)—  
247 viviparous reproduction is associated with maternal and embryonic exposure to foreign tissues,  
248 which is likely to require enhanced regulation of maternal-fetal immune systems.

249

## 250 **II. Length of Embryonic Retention**

251

252 Viviparous amniotes retain the embryo until it is fully developed, but oviparous amniotes  
253 retain the embryo for a fraction of that time. Rather than using precocious hatching and  
254 parturition (PH&P), like that of opossums and early viviparous mammals (Wagner et al., 2014),  
255 squamates evolve viviparity through extended egg retention (García-Collazo et al., 2012; Shine,  
256 1983). Thus, processes affecting the length of embryonic retention are expected to change to  
257 support transitions between parity modes (van Dyke et al., 2014).

258

### 259(1) *Parturition & oviposition*

260 The genes and hormones involved with initiating and ending gestation may provide insights  
261 into the tools squamates can co-opt to change the length of embryonic retention during parity

262 mode transitions. Parturition terminates embryonic retention. Parturition can be divided into four  
263 parts (Terzidou, 2007; Vannuccini et al., 2016)—quiescence (Phase 0), activation (Phase 1),  
264 stimulation (Phase 2) and involution (Phase 3). In eutherian mammals, several processes  
265 contribute to the initiation and termination of gestation including inflammation (Challis et al.,  
266 2009; Hansen et al., 2017), maternal recognition of pregnancy (MRP), mechanical stretch of  
267 uterine tissues (Sooranna et al., 2004; Shynlova et al., 2008), and fluctuating concentrations of  
268 corticotropin-releasing hormone, progesterone, and estrogen (Challis et al., 2000; Condon et al.,  
269 2004; Shaw & Renfree, 2001).

270

271 (i) *Quiescence & sustained progesterone production in reproductive tissues*

272 Extended embryonic retention could be achieved by triggering mechanisms that extend  
273 uterine quiescence, inactivity of the uterus. Inhibition of myometrial contractions through  
274 sustained progesterone production supports quiescence across different viviparous amniotes  
275 (Bazer, 1992; Casey & MacDonald, 1997; Fergusson & Bradshaw, 1991; Ilicic et al., 2017;  
276 Murphy & Thompson, 2011; Putnam et al., 1991; Soloff et al., 2011). The corpus luteum (or  
277 plurally called corpora lutea), a transient progesterone-producing organ, produces progesterone  
278 during gestation. Extended lifespan of the corpus luteum likely aided the evolution of viviparity  
279 in mammals (Amoroso, 1968; Callard et al., 1992; Stouffer & Hennebold, 2015). Thus, early  
280 research on squamate viviparity also explored the influence of corpus luteum lifespan. The  
281 lifespan of corpora lutea associates with oviparous egg retention and oviposition (Diaz, Alonso-  
282 Gomez & Delgado, 1994; Fox & Guillette 1987; Jones & Guillette 1982). Eggshell formation in  
283 oviparous Whiptail lizards, *Cnemidophorus uniparens*, is even disrupted by experimental  
284 removal of corpora lutea (Cuellar, 1979). The lifespan of corpora lutea do not consistently



285 correlate with length of embryonic retention in viviparous squamates like it does in mammals  
286 (Albergotti & Guillette, 2011; Callard et al., 1992).

287 Maternal recognition of pregnancy (MRP) refers to the early signaling of the embryo to  
288 prevent luteolysis (Thatcher, Meyer, & Danet-Desnoyers, 1995), degradation of the corpus  
289 luteum. Luteolysis occurs in the absence of pregnancy. MRP enables continued progesterone  
290 production by the corpus luteum to support uterine quiescence during early gestation. An  
291 independent evolution of MRP is reported for Macropodidae, a lineage of marsupial mammals  
292 (Freyer, Zeller, & Renfree, 2003), and endometrial recognition of pregnancy is recognized in the  
293 opossum (Griffith et al., 2019). MRP has not been explicitly studied in squamates. However,  
294 MRP likely happens in squamates, given that corpora lutea do not get degraded in the earliest  
295 stages of gravidity/gestation in oviparous or viviparous squamates (Callard et al., 1992;  
296 Albergotti & Guillette, 2011).

297 Different genes are signaled by embryos for MRP across mammals. Human chorionic  
298 gonadotropin hormone (hCG) establishes MRP (Ross, 1979; Behrman et al., 1993; Duncan,  
299 McNeilly, & Illingworth, 1998; Duncan, 2000; Ticconi et al., 2007). In pigs, MRP is  
300 hypothesized to be triggered by collaborative signaling of estradiol (E2) and prostaglandins  
301 (PGs) (Geisert et al., 2023). Similarly, glycoproteins, estradiol and prostaglandin E2 (PGE2)  
302 have been implicated in signaling MRP in horses (Klein & Troedsson, 2011; Klein, 2016). In  
303 ruminants, embryonic signaling of IFN- $\tau$  establishes MRP (Bazer, 2013; Bazer, Spencer & Ott,  
304 1997; Thatcher et al., 1995). During gestation in the uterus of viviparous African Ocellated  
305 skinks, *Chalcides ocellatus*, four receptors for interferon alpha, beta, omega, and gamma are  
306 differentially expressed but no expression of IFN- $\tau$  was detected compared to non-gestational  
307 uterine tissue (Brandley et al., 2012). I was unable to find expression patterns of MRP signaling

308 homologs in other squamate reproductive tissues. Should MRP occur in squamates, it may be  
309 signaled by genes that are clade-specific, like in mammals. This makes comparatively evaluating  
310 the influence of MRP on the evolution of viviparity an interesting avenue for future research.

311 The evolution of viviparous extended embryonic retention may be sufficiently supported by  
312 maintenance of chorioallantoic progesterone production coupled with eggshell loss (Griffith,  
313 Brandley et al., 2017). This theory may be broadly applicable across amniotes given that the  
314 most recent common ancestor of amniotes likely had a chorioallantois with an endocrine  
315 function (Griffith, Brandley et al., 2017). Following death of the corpus luteum during gestation,  
316 placental progesterone production supports extended embryonic retention in eutherian mammals  
317 (Castracane & Goldzieher, 1986; Ellinwood et al., 1989; Nakajima et al., 1991; Rothchild, 2003;  
318 Spencer & Bazer, 2004). Viviparous Italian Three-toed Skinks, *Chalcides chalcides*, shift to  
319 chorioallantoic progesterone production following degradation of corpora lutea during gestation  
320 (Guarino et al., 1998). The placenta of viviparous Southern Snow Skinks, *Carinascincus*  
321 *microlepidotus*, produces minimal progesterone but has a strong capacity to convert  
322 pregnenolone to progesterone (Girling & Jones, 2003). Whereas all genes involved with a known  
323 biosynthesis pathway for progesterone production are expressed in the placenta of horses, *Equus*  
324 *caballus*, only some of these genes were detected in the chorioallantois of chickens, *Gallus*  
325 *gallus*, viviparous Southern Grass Skinks, *Pseudemoia entrecasteauxii*, and oviparous and  
326 viviparous Southeastern Sliders, *Lerista bougainvillii* (Griffith, Brandley et al., 2017). Thus, if  
327 chorioallantoic progesterone production has supported multiple origins of viviparity in amniotes,  
328 it is not evidenced by a conserved ancestral gene expression pattern for the biosynthesis of  
329 progesterone (Griffith, Brandley et al., 2017). Nonetheless, parity trait genes in a reproductively

330 bimodal lizard, *Zootoca vivipara*, are associated with progesterone-binding functions (Recknagel  
331 et al., 2021a)—highlighting the role of progesterone in squamate reproduction.

332 Other female reproductive tissues in squamates express genes involved with progesterone  
333 biosynthesis—StAR-related lipid transfer domain protein 3 (*StARD3*) and hydroxy-delta-5-  
334 steroid dehydrogenase (*HSD3B1*). *STARD3* is significantly upregulated in the uterine tissue  
335 during pregnancy in viviparous African Ocellated skinks, *Chalcides ocellatus*, along with  
336 significant differential expression of seven paralogs (Brandley et al., 2012). While *StARD3* is  
337 expressed during gestation in *Zootoca vivipara*, it is not significant differentially expressed  
338 compared to oviparous counterparts; *HSD3B1*, on the other hand, is significantly upregulated  
339 during mid-gestation (Recknagel et al., 2021a). Compared to non-gestational samples, *HSD3B1*  
340 is significantly upregulated in the uterus during early and late gestation in viviparous individuals  
341 of reproductively bimodal *Saiphos equalis* (Foster et al., 2020). Oviparous individuals from the  
342 same species did not exhibit this expression pattern (Foster et al., 2020). Activity of *HSD3B1*  
343 was detected in the mucosal epithelium of oviparous Eastern Garden Lizards, *Calotes versicolor*  
344 (Kumari et al., 1992), and in the uterine glands of oviparous Keeled Indian Mabuya, *Eutropis*  
345 *carinata* (Mundkur & Sarkar, 1982). Other genes involved with the biosynthesis of progesterone  
346 (e.g., steroidogenic acute regulatory protein or cytochrome-P450-family-11-subfamily-A-  
347 polypeptide-1) serve as further candidates for exploring the relationship between organ-specific  
348 patterns of progesterone production and the evolution of extended embryonic retention in  
349 viviparous squamates.

350 For progesterone to prevent myometrial contractions and support quiescence, there must be  
351 progesterone receptors (PGRs) in the uterus (Mesiano et al., 2011; Young et al., 2011). In  
352 humans, progesterone responsiveness is related to specific ratios of PGRs, *PR-A* and *PR-B*, in

353 myometrial cells (Young et al., 2011). Minimal research exists on PGR expression in squamate  
354 reproductive tissues. One study found that in the uterus of the yolk-sac in viviparous Southern  
355 Grass Skinks, *Pseudemoia entrecasteauxii*, one progesterone receptor, *PGRMC2*, is upregulated  
356 compared to non-gestational uterine tissue (Griffith et al., 2016); Another progesterone receptor,  
357 *PGR*, is downregulated in the uterus of the chorioallantoic placenta and yolk sac placenta  
358 compared to non-gestational uterine tissue (Griffith et al., 2016). Downregulation of both *PGR*  
359 and *PGRMC2* in the uterus during gestation was detected in viviparous *Chalcides ocellatus*  
360 (Brandley et al., 2012). While *PGR* is differentially expressed at mid-gestation in viviparous  
361 individuals compared to oviparous, *PGRMC1* and *PGRMC2* are not differentially expressed  
362 (Recknagel et al., 2021a). However, admixture mapping revealed three SNPs most highly  
363 associated with gestation length in *Zootoca vivipara* are located in close proximity to *PGRMC1*  
364 (Recknagel et al, 2021a). Measuring expression of PGRs and their ratios in uteruses of  
365 oviparous and viviparous squamates will help elucidate the receptors needed to support  
366 progesterone responsiveness in squamate uteruses and their relationship to extended embryonic  
367 retention.

368

369 (ii) *Activation & progesterone withdrawal*

370 The activation stage of parturition is marked by the withdrawal, or functional withdrawal, of  
371 progesterone leading to an estrogen dominated response during the next state, stimulation  
372 (Bakker, Pierce, & Myers, 2017; Fergusson & Bradshaw, 1991). Progesterone may withdraw in  
373 response to environmental stimuli in reptiles during parturition (Shine & Guillette, 1988). In  
374 mammals, activation is marked by increasing concentrations of corticotropin-releasing hormone  
375 and contraction associated proteins (CAPs) including connexin-43, prostaglandins, oxytocin

376 receptors, prostanoid receptors and cell signaling proteins (Bakker et al., 2017; Ilicic et al., 2017;  
377 Leadon et al., 1982; Pashen & Allen, 1979; Whittle et al., 2000). Pro-inflammatory cytokines  
378 and chemokines, prostaglandin synthase-2 (*COX-2*, also referred to as *PTGS2*), and NF-κB also  
379 influence activation in mammals (Christiaens et al., 2008; Lappas et al., 2002; Lappas & Rice,  
380 2007; Lindström & Bennett, 2005; Olson, 2003; Terzidou, 2007).

381 Some similar patterns are associated with oviposition in birds. In chickens, *Gallus gallus*,  
382 prostaglandin F (PGF) concentrations increase in the hours leading up to oviposition (Takahashi  
383 et al., 2004). Experimental injection of oxytocin and arginine vasotocin (AVT), similar  
384 neurohypophyseal peptides, revealed that uterine tissues of chickens, *Gallus gallus*, maintain  
385 responsiveness to oxytocin but are more sensitive toward arginine vasotocin (Ewy, 1970).  
386 Murphy & Thompson (2011) provide a rather exhaustive list of resources on progesterone and  
387 estrogen assays across oviparous and viviparous squamates. Future research should consider  
388 exploring parallels between mechanisms of activation in mammals and squamates. Any process  
389 that can trigger or stall activation should lead to extended embryonic retention.

390

391 (iii) *Stimulation & electrical gradients, inflammation, and hormonal regulation*

392 Mechanical stretch, electrical gradients, inflammatory processes, and hormonal regulation  
393 contribute to stimulation, the phase when contractions, cervical ripening and dilation occur.  
394 Stimulation involves contributions from maternal and fetal tissues. As early as 460 BC there was  
395 uncertainty over the proportional influence of mother or fetus on the initiation of parturition.  
396 Hippocrates proposed that the fetus initiates parturition by pushing its feet on the fundus of the  
397 uterus. Although the reality is not so cartoonish, mechanical stretch of the uterus from the

398 growing embryo plays a role in parturition (Lefebvre et al., 1995; Tamizian & Arulkumaran,  
399 2004; Wray et al., 2015).

400 Physical stretching of the uterus causes an influx of calcium and sodium, altering the action  
401 potential and enabling contractions (Kao & McCullough, 1975). Calcium further activates  
402 voltage gated calcium channels on myometrial cell membranes, enhancing the influx of calcium  
403 ions, mediating the force and speed of myometrial contractility (Arrowsmith & Wray, 2014;  
404 Wray et al., 2015). The influence of uterine overdistention on partition in birds and non-avian  
405 reptiles has not yet been examined, to my knowledge. However, differentially expressed genes  
406 functionally enriched the GO term for “voltage-gated calcium channel activity” in uterine tissues  
407 during gravidity and gestation in *Saiphos equalis* (Foster et al., 2020). A uterine response to  
408 overdistention is among the many possible explanations for this. It may be important to consider  
409 the influence of uterine overdistention on squamate parity mode transitions, because should  
410 bioelectrical responses to uterine overdistention be a common feature of vertebrate parturition,  
411 lessened distention may be a hurdle to reverse back to oviparity. Uterine overdistention may  
412 influence parturition by triggering an “inflammatory pulse” that activates further myometrial  
413 contractility, which leads to preterm birth in primates (Adams Waldorf et al., 2015).

414 During parturition, there is an influx of uterine and embryonic pro-inflammatory genes and  
415 immune cells (Adams Waldorf et al., 2015; Charpigny et al., 2003; Mesiano et al., 2002; Park et  
416 al., 2005). Uterine contractions in humans involve actions of prostaglandins (PGs), oxytocin,  
417 corticotropin-releasing hormone, cytokines, and neutrophils (Adams Waldorf et al., 2015; De  
418 Rensis et al., 2012; Olson & Hertelendy, 1983; Park et al., 2005; Sykes et al., 2014; Terzidou,  
419 2007).

420 The cycling concentrations of a neuropeptide, corticotropin-releasing hormone (CRH),  
421 supports parturition in humans. This has been compared to a biological clock that is initiated at  
422 early stages of gestation (Lockwood, 2004; McLean & Smith, 2001). Increased production of  
423 CRH facilitates parturition by interacting with CRH receptors, CRH-R1 and CRH-R2, which are  
424 suggested to promote myometrial relaxation or contractility, respectively (Hillhouse &  
425 Grammatopoulos, 2001). Altered regulation, phenotype or function of hormones that function as  
426 biological clocks, like CRH, may have a particularly strong influence on evolutionary changes to  
427 length of embryonic retention, a trait inherently related to time.

428 Placental CRH production has only been identified in primates thus far (Challis et al., 2005;  
429 Emanuel et al., 1994; Florio et al., 2002; Hillhouse & Grammatopoulos, 2001; Karteris et al.,  
430 1998; Mendelson, 2009; Robinson et al., 1989). Placental CRH production may, therefore, be  
431 unique to primates. However, the amino acid sequence of CRH is highly conserved in vertebrates  
432 (Noy et al., 2017), indicating there is a possibility for shared function across diverse taxa. Like  
433 CRH cycling in mammals, timely fluctuations of AVT stimulates uterine contractions, enables  
434 oviposition in birds, turtles, and lizards (Ewy, 1970; Fergusson & Bradshaw, 1991; Guillette Jr &  
435 Jones, 1980; Jones et al., 1987; Rzasa, 1978; Wu et al., 2019).

436 Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) influence, respectively, uterine  
437 contractions and cervical relaxation for partition across many amniotes including humans, *Homo*  
438 *sapiens* (Terzidou, 2007), domestic pigs (De Rensis et al. 2012), domestic chickens (Hertelendy  
439 et al., 1974; Olson et al., 1986), and Loggerhead Sea turtles (Guillette et al., 1991). Injections of  
440 PGF<sub>2α</sub> and PGE<sub>2</sub> induce parturition in viviparous Yarrow's Spiny lizards, *Sceloporus jarrovi*, and  
441 Raukawa geckos, *Woodworthia maculatus* (Cree & Guillette, 1991; Guillette et al., 1992).  
442 However, no injected dosages of PGF<sub>2α</sub> or PGE<sub>2</sub> induced oviposition in oviparous Collard

443 lizards, *Crotaphytus collaris*, Eastern Fence lizards, *Sceloporus undulatus*, Six-lined  
444 racerunners, *Aspidoscelis sexlineatus*, or Striped Plateau lizards, *Sceloporus virgatus* (Guillette et  
445 al., 1991). It is interesting that injections of  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  induced parturition in viviparous  
446 lizards but did not induce oviposition in oviparous lizards studied. Given this, it is plausible that  
447 regulatory or functional changes to  $\text{PGF}_{2\alpha}$  and/or  $\text{PGE}_2$  in squamates could facilitate changes to  
448 the length of embryonic retention to support transitions between reproductive modes. However,  
449 induction of parturition with  $\text{PGF}_{2\alpha}$  in viviparous *Woodworthia maculatus* only worked with  
450 pre-treatment of  $\beta$ -adrenoceptor (Cree & Guillette, 1991).

451  $\text{PGF}_{2\alpha}$  decreases progesterone concentrations during stimulation (De Rensis et al., 2012). In  
452 humans, biosynthesis of PGs is driven largely by the enzyme cyclooxygenase (*COX*)-2 rather  
453 than *COX-1* (i.e., prostaglandin synthase-2 and -1) (Slater et al., 1995, 1999). This helps  
454 maintain the decreased progesterone/estrogen ratio of stimulation. In ovariectomized viviparous  
455 Garter snakes, *Thamnophis*, increased estrogen stimulated thickness of uterine epithelial cells  
456 and glandular activity, whereas administration of progesterone had little influence on uterine  
457 histology (Mead et al., 1981). Uterine pig models revealed that estrogen stimulates involuntary  
458 contraction and relaxation (peristalsis) of the uterus (Mueller et al., 2006).

459 The softening of the cervix is important during the stimulation stage of parturition. A  
460 hormone related to insulin, *relaxin*, promotes myometrial softening in humans, *Homo sapiens*,  
461 domestic pigs, and turtles (Mercado-Simmen et al., 1982; Sorbera et al., 1988; Weiss &  
462 Goldsmith, 2001). The cervix also gets softer by actions of  $\text{PGE}_2$ .  $\text{PGE}_2$  activates pro-  
463 inflammatory cytokines, interleukin (IL)-8 and tumor necrosis factor (TNF)- $\alpha$ , which activates  
464 the collagenases and matrix metalloproteinases for cervical softening (Bakker et al., 2017). This  
465 causes a positive feedback loop between IL-8 and  $\text{PGE}_2$  synthesis (Denison et al., 1998;



466 Denison, Calder & Kelly, 1999; Terzidou, 2007; Li et al., 2010). Upregulated of IL-8 is also  
467 promoted by the protein complex NF-kB during parturition in humans (Elliott, 2001). Similar  
468 patterns were observed during parturition in mice and baboons (Mendelson & Condon, 2005;  
469 Mendelson, 2009).

470 A few studies focus on the role of cytokines on squamate reproduction but not explicitly  
471 during oviposition or parturition (Hendrawan et al., 2017; Paulesu et al., 1995, 2005, 2008).  
472 Some studies detected expression of cytokines during late gestation (Foster et al., 2020; Gao et  
473 al., 2019; Recknagel et al., 2021a). TNF- $\alpha$  related activity was only detected at this time in  
474 viviparous Tussock Cool-skinks, *Pseudemoia entrecasteauxii*, which were found to  
475 downregulate TNF- $\alpha$  induced proteins (*TNFAIP6* and *TNFAIP8L2*) in the ‘uterus of the  
476 chorioallantoic placenta’ and *TNFAIP6*, *TNFAIP1*, and *TNFAIP2* in the ‘uterus of the yolk-sac  
477 placenta’ compared to not gestational uterine tissues (Griffith et al., 2016). Activity of TNF- $\alpha$  in  
478 reproductive tissues during gestation in viviparous Italian Three-toed skinks, *Chalcides*  
479 *chalcides*, and reproductively bimodal European common lizards, *Zootoca vivipara*, was  
480 associated with maternal-fetal immune dynamics (Paulesu et al., 1995, 2005, 2008; Hendrawan  
481 et al., 2017).

482 Altered expression or phenotype of contractility agonists, oxytocin receptors and estrogen  
483 receptors, and contractility antagonists, progesterone receptors and  $\beta$ -adrenergic receptors  
484 (Ravanos et al., 2015) may also change the length of embryonic retention to support transitions  
485 between parity modes. Differences in length of embryonic retention in oviparous and viviparous  
486 agamas, *Phrynocephalus przewalskii* and *Phrynocephalus vlangalii*, appears to be driven by  
487 regulatory differences of prostaglandins, *COX-2*, an AVT receptor (*MTR*),  $\beta$ -adrenergic receptors,  
488 and estrogen receptors. During oviposition, *P. przewalskii*, exhibited the following: promotion of

489 contractions through downregulation of  $\beta$ -adrenergic receptor (*ADRB2*), and upregulation of  
490 *COX-2* and prostaglandin, and absent (potentially lost) expression of two estrogen receptors  
491 (*ESR1* and *ESR2*) and the AVT receptor, *MTR* (Gao et al., 2019). During the stage of gestation  
492 corresponding to oviposition, viviparous sister-species, *P. vlangalii*, exhibited the following  
493 alternate pattern: inhibition of contractions caused by upregulation of *ADRB2* and  
494 downregulation of two estrogen receptors (*ESR1*, *ESR2*), *MTR*, *COX-2*, and prostaglandin (Gao  
495 et al., 2019). Some viviparous squamates, *Saiphos equalis*, *Chalcides ocellatus*, and *Pseudemoia*  
496 *entrecasteauxii*, share some of these expression patterns (*COX-2*, *MTR*, and *ADRB*, respectively)  
497 thought to be involved with extended embryonic retention in viviparous *P. vlangalii* (Brandley et  
498 al., 2012; Foster et al., 2020; Gao et al., 2019; Griffith et al., 2016); and *ADRB2* is upregulated at  
499 mid-gestation in viviparous *Zootoca vivipara* compared to oviparous counterpart (Recknagel et  
500 al., 2021a). Overexpressed genes in viviparous uterine tissues of *Zootoca vivipara* also  
501 functionally enriched pathways for beta 1 and beta 2 adrenergic receptor signaling pathways  
502 (Recknagel et al., 2021a). This study, which compared uterine expression profiles during  
503 gestation across viviparous species of squamates, rodents, canines, ungulates, and humans,  
504 concluded that shared regulatory networks are recruited to support viviparity (Reckangel et al.,  
505 2021a).

506 Recently, in humans, the only Classical Major Histocompatibility Antigen (C-MHC)  
507 expressed by trophoblasts (specialized placental cells) was associated with parturition when it  
508 was discovered that HLA-C is significantly increased during laboring term and preterm placentas  
509 compared to non-laboring placentas (Hackmon et al., 2017). The authors suggested a mechanism  
510 where fetal HLA-C open conformers on the placenta provoke inflammation of maternal tissues,  
511 leading to parturition (Hackmon et al., 2017). Expression of MHC alloantigens, foreign antigens

512 to the host, by fetal cells is also associated with parturition in cows and horses (Benedictusa,  
513 Koets & Ruttena, 2015; Davies et al., 2004; Joosten et al., 1991; Rapacz-Leonard et al., 2018).  
514 Around one month prior to parturition in cows, endometrial epithelium thins and eventually  
515 disappears completely, putting the antigen-presenting trophoblasts (Adams et al., 2007) in  
516 contact with maternal connective tissue of the endometrium (Podhalicz-Dzięgielewska et al.,  
517 2000). Fetal MHC alloantigens are proposed to promote the loosening of maternal and fetal  
518 tissues (Benedictusa et al., 2015). MHC molecules are expressed during gestation in some  
519 squamates (Murphy, Thompson & Belov, 2009) but their role in oviposition or parturition has  
520 not yet been considered to my knowledge. Identifying the presence or absence of MHC  
521 alloantigens on embryonic tissues before and during parition across more diverse taxa may  
522 reveal how ubiquitous the influence of embryonic MHC molecules is on this.

523       Involution (phase 3) occurs after the embryo(s) is released. In eutherian involution, the  
524 placenta detaches, and the uterus shrinks. This is supported by actions of prostaglandins  
525 (Husslein, 1984) and oxytocin (Terzidou, 2007). It seems unlikely for processes of involution to  
526 be related to evolutionary changes to the length of embryonic retention.

527

## 528       (2) *Unique qualities of oviposition & parturition in Sauropsids*

529       The physiology of avian oviposition is dependent on a circadian schedule (Williams, 2012).  
530 A general model of an “open period”, when eggs are laid are separated by “laying gaps”  
531 (Williams, 2012). Chicken ovulation and oviposition cycles leave an 8-hour open period where  
532 luteinizing hormone (LH) and progesterone surge, initiating ovulation and continuing the cycle.  
533 At the extreme, the ancient murrelet, *Synthliboramphus antiquus*, oviposits a two-egg clutch on  
534 seven-day intervals (Williams, 2012). Longer laying intervals have been associated with longer

535 intervals between initiation of yolk development (Astheimer & Grau, 1990). Differing from  
536 birds, oviparous squamates retain eggs longer than the ovarian cycle (Tinkle & Gibbons, 1977).  
537 This suggests that oviparous squamates may rely on different molecular mechanisms to support  
538 oviposition than birds.

539 Non-avian reptiles are unique in that they are the only ectothermic amniotes. This makes  
540 them uniquely reliant on temperature for embryonic retention and associated embryonic  
541 signaling to indicate the stage of embryonic development. Additionally unique, gemales are the  
542 heterogametic sex in several squamates, leading some research to suggest chromosome linkage  
543 evolution may increase the speed of evolution in genes associated with gestation length  
544 (Recknagel et al., 2021a). Admixture mapping, made possible by the natural hybridization of  
545 oviparous and viviparous populations of *Zootoca vivipara*, revealed 439 candidate genes  
546 associated with embryonic retention (Recknagel et al., 2021a). Eleven of these genes were also  
547 associated with eggshell traits (Recknagel et al., 2021a)—underscoring the pleiotropic roles of  
548 some genes putatively involved in squamate parity mode evolution.

549

### 550(3) *Pre-term birth & embryonic retention mechanisms*

551 The literature on pre-term birth may be a fruitful avenue of research to inform understanding  
552 on the evolutionary genomics of embryonic retention length. Slower increases of CRH (Ellis et  
553 al., 2002) and higher expression of Neurokinin B, for example, are associated with pre-term birth  
554 in humans (Torricelli et al., 2007). Injections of RU486, a progesterone receptor (PGR)  
555 antagonist, promoted pre-term labor in rhesus macaques but the progression of physiological  
556 activity differed from normal parturition (Haluska et al., 1987). Examining homologs of genes  
557 involved with human pre-term birth in squamates may provide further candidates for genes that

558 could impact the length of embryonic retention in squamates. Some evolutionary studies are  
559 taking implications of pre-term birth into account. For example, a comparative evolutionary  
560 transcriptomics study across therians, monotremes, squamates, and an amphibian recently  
561 associated *HAND2* with preterm birth in Eutherian mammals (Marinić et al., 2021).

562 In humans, pregnancy loss from infection follows distorted ratios of immune factors at the  
563 maternal-fetal interface (Arenas-Hernandez et al., 2016; Chaturvedi et al., 2015; Chattopadhyay  
564 et al., 2010). Future research on the evolution of lengthened embryonic retention to support  
565 viviparity may benefit from exploring ratios of immune cells in the uterus and embryonic tissues  
566 during term and pre-term pregnancy in squamates. I direct researchers to the literature on the  
567 reptile immune system and immune cell ratios at the maternal fetal interface during term and pre-  
568 term mammalian pregnancy for further exploration (Yang et al., 2019; Zimmerman, 2010, 2020).

569

#### 570(4) *Discussion & future directions—embryonic retention and parity mode evolution*

571 The physiological processes involved with the start of gestation (maternal recognition of  
572 pregnancy) and the end of gestation (partition) in birds and mammals provide insights into the  
573 genes and hormones squamates may co-opt to alter length of embryonic retention during  
574 transitions between parity modes. Unsurprisingly, hormones like estrogen and progesterone, play  
575 important roles in partition across amniotes. Further processes to be examined in squamates  
576 include signaling of homologous genes for MRP, placental progesterone production, novel  
577 pathways for biosynthesis of progesterone, the role of beta 1 and beta 2 adrenergic receptor  
578 signaling pathways, fluctuating ratios of progesterone receptors, the lifespan of the corpus  
579 luteum across a broader range of taxa, production and circulation of homologs for AVT and  
580 CRH or other similarly structured genes, expression of fetal alloantigens and inflammatory

581 cytokines in utero, and the influence of uterine overdistention on contractions. Regarding  
582 squamate parity mode transitions, the role of uterine overdistention in mammalian parturition  
583 suggests a lack of uterine overdistention may be one hurdle for reversals back to oviparity.  
584 Understanding the evolutionary physiology and genomics of embryonic retention in oviparous  
585 and viviparous squamates will benefit from focused attention on reproductively bimodal species  
586 (Whittington et al., 2022) and from genomics/physiological research across more taxa that vary  
587 in reproductive modes.

588

### 589 **III. Eggshell Formation**

590

591 Oviparous amniotic embryos develop within an eggshell that is at least partially  
592 mineralized, whereas viviparous embryos generally do not. Primarily, the eggshell serves as  
593 physical protection and calcium reserve (Stewart & Ecy 2010; Stewart et al., 2009). The  
594 eggshell matrix contains immune properties and pores that enable gas exchange and water uptake  
595 (Packard et al., 1982). Evolutionary transitions between parity modes therefore requires changes  
596 to the process of eggshell formation. The history of research on the evolutionary morphology of  
597 the amniote egg is important for future comparative research (Blackburn & Stewart, 2021). Some  
598 have suggested that the amniote eggshell originated multiple times (Aoki, 1993).

599 Birds have hard calcareous eggshells. Other than two lineages of geckos with hard shells,  
600 oviparous squamates have parchment-shelled eggs with a thin layer of calcium deposits on the  
601 outer surface of the shell membrane (Blackburn & Stewart, 2021; Choi et al., 2018).  
602 Monotremata (egg-laying mammals) have an eggshell but far less has been documented about its  
603 structure compared to other amniotes (Legendre et al., 2022). The structure and physiological

604 mechanisms involved with eggshell calcification are most well resolved in birds (Choi et al.,  
605 2018; Francesch et al., 1997; Jonchère et al., 2010, 2012; Rose-Martel, Du, & Hincke, 2012).  
606 Eggshell deposition in tuatara and squamates differs dramatically (Choi et al., 2018). Viviparous  
607 squamates lack an eggshell, absorb the eggshell during gestation, or have a thin layer of calcium  
608 deposits.

609         The earliest records of amniote eggshells have features characteristics of Archelosaur  
610 eggshells, including the mammillary layer (Stein et al., 2019; Legendre et al., 2022). Recent  
611 reconstructions are consistent with a thin eggshell in ancestral dinosaurs (Norell et al., 2020;  
612 Stein et al., 2019). It is important to consider that the semi-rigid shells of Lepidosaur and  
613 testudines are not homologous (Legendre et al., 2022); the microstructure of Archelosauria  
614 (birds, crocodiles, turtles and dinosaurs) and Lepidosaur eggshells are remarkably different (Choi  
615 et al., 2018); and recent reconstructions of the composition and ultrastructure of dinosaur  
616 eggshells revealed that calcified hard eggshell of dinosaurs originated three times (Norell et al.,  
617 2020). In the remainder of this section, I consider how structural, mineral,  
618 genomic/transcriptomic, and proteomic information on amniote eggshells can inform scientific  
619 understanding of the ancestral eggshell of amniotes and Lepidosaur.

620         The genetic drivers of eggshell formation are not resolved in squamates. Two oviparous  
621 lizards, *Lerista bougainvillii* and *Lampropholis guichenoti*, differentially express either zero or  
622 two genes, respectively, in utero in non-gravid vs gravid comparisons (Griffith et al., 2016).  
623 However, this study only measured gene expression at one developmental stage, making it  
624 difficult to infer if regulatory changes influence eggshell formation. Nonetheless, oviparous  
625 *Saiphos equalis* and *Phrynocephalus przewalskii* have extensive differential expression during  
626 gravidity (Foster et al., 2020; Gao et al 2019). It is interesting to see drastically different uterine

627 gene expression profiles associated with oviparity, given that shared genes are recruited to the  
628 uterus to support viviparity across diverse amniotes (Recknagel et al., 2021a). Under the  
629 assumption that conserved traits should be accompanied with more similar gene expression  
630 profiles than convergent traits, uterine gene expression profiles in themselves currently reveal  
631 more conserved regulatory networks in utero for squamate viviparity than oviparity.

632         Some genetically determined traits are known to be evolutionarily labile in squamates, like  
633 venom and limb reduction (Camaiti et al., 2021; Sites et al., 2011). In *Saiphos equalis*, shell  
634 characteristics of facultatively partitioned oviparous and viviparous embryos are similar, leading  
635 authors to infer that both parity modes utilize the same machinery to produce egg coverings  
636 (Laird et al., 2019). In this species, environmental influences on gestation length, rather than  
637 genetic influences on eggshell thickness, may play a more dominant role in parity mode  
638 evolution (Laird et al., 2019). In *Zootoca vivipara*, Recknagel et al. (2021a) identified 38  
639 candidate genes associated with eggshell traits and concluded that the genetic architecture of  
640 eggshell traits is simpler than that of gestation length.

641

#### 642         (1) *Mineral composition of eggshells*

643         The different mineral compositions of eggshells across amniotes may provide insight into the  
644 differing physiological conditions and evolutionary histories under which they are formed (Table  
645 1). Taxa use a polymorph of calcium carbonate—calcite, aragonite or vaterite—to develop the  
646 eggshell (Hincke et al., 2012). Amorphous calcium carbonate (ACC) is a transient non-  
647 crystalline precursor phase of calcite and aragonite that is important for many calcification  
648 processes in invertebrates (Hincke et al., 2012). It was recently shown to control avian eggshell  
649 mineralization (Rodríguez-Navarro et al., 2015).



650 In birds, the organic components of uterine fluid promote the formation of calcite  
 651 (Hernández-Hernández, Gomez-Morales et al., 2008; Hernández-Hernández, Rodriguez, et al.,  
 652 2008; Hernández-Hernández, Vidal et al., 2008). Most amniotes use this polymorph (Hernández-  
 653 Hernández, Gomez-Morales et al., 2008; Hernández-Hernández, Rodriguez, et al., 2008;  
 654 Legendre et al., 2022). However, turtle eggshells are predominately developed with aragonite  
 655 (Choi et al., 2022; Mikhailov, 1997). The eggshell of most squamates consists of an inner fibrous  
 656 protein layer overlain by calcium carbonate that can be a single layer or scattered crystals (Choi  
 657 et al., 2018; Packard & DeMarco, 1991; Stewart et al., 2010).

658 There are differing accounts on the microstructure of monotreme eggshells, however  
 659 conceptus coats include three layers including zona pellucida, mocooid coat and shell coat  
 660 (Frankenberg & Renfree, 2018). Further studies are needed test for secondary homology.  
 661 Monotreme shells are described as proteinaceous, permeable, and flexible (Hughes, 1984).  
 662 Marsupials lack an eggshell but have an eggshell coat, similar to that of monotremes  
 663 (Frankenberg & Renfree, 2018), that is secreted by the epithelial cells and endometrial glands  
 664 early on in embryonic development prior to implantation (Roberts et al., 1994; Roberts & Breed,  
 665 1996). Upon hatching of the shell coat and attachment of the embryo, a cooperative  
 666 inflammatory response ensues (Stadtmauer et al., 2020a, 2020b).

667 **Table 1.** Amniote Eggshell Ultrastructures

Taxon	Eggshell ultrastructure
Testudoid	Radial aragonite with organic core at base
Crocodiloid	Tabular, arranged in wedges of calcite with no organic core
Squamate	Two types: <ul style="list-style-type: none"> <li>• rigid-shelled eggs with well-developed crystalline layer (dibamid and gekkonid lizards). Stem-like crystals grow downward making for a rigid shell</li> <li>• flexible-shelled eggs with parchment-like shell of fibrils overlaid with little thin crystal caps or no crystalline material (other squamates)</li> </ul>
Ornithoid (avian)	Calcite with a clear boundary between lower and upper parts. Mammillary layer defines the lower portion of the shell, with calcite crystals that radiate upwards
Monotreme	Distensible, permeable and highly proteinaceous

668 Note: Adapted from Choi et al., (2018); Frankenberg & Renfree, (2018); Hallman & Griebeler, (2015); Hincke et  
669 al., (2012); Trauth & Fagerberg, (1984)

670

671

672 (2) *Uterine glands & the evolution of parity modes*

673 Eggshell formation occurs in the uterus where the uterine glands secrete precursors of the  
674 eggshell (Girling, 2002; Guillette, Fox & Palmer, 1989; Jonchère et al., 2010; Nys et al., 2004;  
675 Picariello et al., 1989; Stewart & Eca, 2010). Uterine glands are critical for gravidity/gestation  
676 in both oviparous and viviparous amniotes (Braz et al., 2018; Burton et al., 2002; Cooke et al.,  
677 2013). For example, in humans, uterine glands provide histiotrophic nutrition to the early  
678 embryo (Burton et al., 2002). In reptiles, precursors for the proteinaceous eggshell membrane are  
679 secreted by the uterine glands (Corso, Delitala & Carcupino, 2000; Heulin et al., 2005; Palmer et  
680 al., 1993). Calcium secretion can also involve uterine epithelial cells (Herbert, Thompson &  
681 Lindsay, 2006; Thompson et al., 2007). Uterine epithelium of the soft-shelled turtle, *Lissemys*  
682 *punctata punctata*, and the eastern collard skink, *Chrotaphytus collaris* stain positive for calcium  
683 (Guillette et al., 1989; Sarkar et al., 1995).

684 Viviparous squamates have an absent or reduced eggshell membrane to facilitate gas  
685 exchange (Blackburn, 1993; Braz et al., 2018) Some squamates are encased in the thin  
686 membrane through the entirety of development like the viviparous lizard, *Zootoca vivipara*  
687 (Heulin, 1989). Others have the membrane only in the early stages of embryonic development  
688 like in garter snakes *Thamnophis radix* and *T. sirtalis* (Blackburn & Lorenz, 2003). Calcium  
689 deposits are detected on the outer surface of the membrane throughout development in other  
690 viviparous lizards (Stewart et al., 2013).

691 Reduced number or size of eggshell glands leads to reduced eggshell membrane thickness in  
692 viviparous squamates. In chickens, variation in size, spacing, and neutron density of eggshell  
693 glands may also be important for eggshell structure (Guillette & Jones, 1985). In the

694 reproductively bimodal Yellow-bellied three toed skink, *Saiphos equalis*, the density of eggshell  
695 glands plays a role in eggshell thickness (Stewart et al., 2010). In the reproductively bimodal  
696 lizard, *Zootoca vivipara*, viviparous individuals have a uterine glandular layer that is less  
697 developed during the stage of eggshell formation compared to oviparous individuals (Heulin et  
698 al., 2005). Additionally, in *Lerista fragilis*, which lays eggs that hatch within just hours of  
699 oviposition, the uterus contains very few mucosal glands (Guillette, 1992). In the fence lizard,  
700 *Sceloporus a. aeneus*, the irregular surface of the eggshell was attributed to the irregular spacing  
701 of shell glands (Guillette & Jones, 1985). In an oviparous gecko, *Hemidactylus turcicus*, their  
702 eggshell glands have loosely packed secretory granules that produce a hard, calcareous shell  
703 (Girling et al., 1998). In a comparison of oviparous and viviparous water snakes from the genus  
704 *Helicops*, viviparous embryos have thinner shell membranes which associated with reduced size  
705 of eggshell glands (Braz et al., 2018). In an oviparous gecko, *Saltuarius wyberba*, their secretory  
706 granules are tightly packed, and their shell is soft and parchmentlike (Girling et al., 1998). In a  
707 viviparous relative, *Hoplodactylus maculatus*, there are far fewer eggshell glands, and where  
708 there are glands, the secretory granules are smaller and more electron dense (Girling, Cree &  
709 Guillette, 1997; Girling, Cree & Guillette, 1998). Smaller eggshell gland size during or after  
710 vitellogenesis is also found in other viviparous squamates compared to oviparous counterparts  
711 (Braz et al., 2018; Gao et al., 2019; Heulin et al., 2005). To my knowledge, in monotremes the  
712 relationship between eggshell thickness and shell gland size, density or compaction of secretory  
713 granules has not been explored.

714 In the oviparous Przewalski's toadhead agama lizard, *Phrynocephalus przewalskii*, 148 genes  
715 are highly expressed in the uterus during the stage of eggshell gland development (Gao et al.,  
716 2019). Only three of these are highly expressed in *P. vlangalii*, a viviparous close relative at this

717 time, suggesting differences in oviparous and viviparous eggshell gland development requires  
718 regulatory changes to dozens of genes (Gao et al., 2019). In the opossum, a marsupial,  
719 proliferation of uterine glands is not induced by the conceptus (Griffith et al., 2019).

720

### 721 (3) *Evolutionary implications of the physiology of eggshell formation*

722 Presumably because of the influence it has on food production, the process of eggshell  
723 formation has been studied most extensively in chickens (Hincke et al., 2012). The avian  
724 eggshell is formed in a cell-free environment, and it is the fastest calcifying process known to  
725 biology (Hincke et al., 2012; Rodríguez-Navarro et al., 2015). During eggshell formation in  
726 birds, uterine fluid containing a supersaturation of ionized calcium and bicarbonate ions  
727 surrounds the egg (Nys et al., 1991). Transport of calcium in the uterus correlates with plasma  
728 membrane  $\text{Ca}^{2+}$ -ATPase (*PMCA*) activity and with concentrations of calbindin-D28K within  
729 shell gland epithelial cells (Herbert et al., 2006; Wasserman et al., 1991). This leads to the  
730 spontaneous precipitation of calcium carbonate into calcite (Hincke et al., 2012). In the  
731 oviparous lizard, *Lampropholis guichenoti*, immunofluorescence microscopy revealed activity of  
732 *PMCA* in the uterus at the time of eggshell calcification (Thompson et al., 2007).

733 Eggshell formation begins with the eggshell membrane. Two unciliated cell types in the  
734 uterus contribute to eggshell membrane formation in a viviparous skink, *Chalcides ocellatus*  
735 *tiligugu* (Corso et al., 2000). One secretes sulfated glycosaminoglycans to form the inner shell  
736 membrane, and the other which secretes acidic glycoproteins to form the outer layers (Corso et  
737 al., 2000). Simple alveolar glands in the lamina propria secrete collagen fibers (Corso et al.,  
738 2000). Inhibition of fiber formation or cross-linking, typically caused by aminopropionitrile or a

739 copper deficiency, causes distorted formations of the eggshell membrane in birds (Arias et al.,  
740 1997; Chowdhury & Davis, 1995; Hincke et al., 2012).

741 In characteristic Archelosaur eggshells (Choi et al., 2018; Legendre et al., 2022), organic  
742 aggregates are deposited onto the shell membrane creating mammillary knobs, which are absent  
743 in Lepidosaur shells (Choi et al., 2018). Mammillary knobs are a distinct layer between the outer  
744 eggshell membrane and the calcified shell matrix layer (Hamilton, 1986). Part of the mammillary  
745 knobs, called basal caps, are embedded into the outer eggshell membrane fibers (Tyler, 1965).  
746 Mammillary knobs serve as regions of crystal initiation where ACC is deposited (Gautron et al.,  
747 2021) and converted into calcite crystals with no intermediate phase (Rodríguez-Navarro et al.,  
748 2015). Cones are formed that radiate in all upward directions, extending up to the shell matrix  
749 layer (Tyler, 1965). Despite the direct relationship between mammillary knobs and calcium  
750 carbonate crystallization (Rao et al., 2015), the protein comprising mammillary knobs remains  
751 uncharacterized. A keratan sulfate (KS)-proteoglycan, “mammillan”, has been implicated in the  
752 composition of mammillary knobs (Fernandez et al., 2001; Hincke et al., 2012). Any given  
753 proteoglycan is a product of multiple coding genes and biosynthesis of KS-proteoglycans is non-  
754 trivial (Caterson & Melrose, 2018; Funderburgh, 2002; Iozzo et al., 2015). However,  
755 investigations into the keratan sulfate proteoglycan proposed as “mammillan” and identifying its  
756 Properties that Facilitate Calcium Deposition (P-FCD) has far reaching implications given that  
757 KS-proteoglycans are proving to be important players in neurological and cancer research  
758 (Leiphrakpam et al., 2019). The role of homologs of “mammillan” in eggshell formation in  
759 squamates may reveal more about the evolutionary history of the eggshell in amniotes.

760 Parsimony would suggest that all oviparous amniotes shared an ancestral process of  
761 eggshell formation. In Archelosaurs, the process of eggshell formation relies on mammillary

762 knobs and upward growth of calcite, as described above. In Lepidosaur eggshells, which have  
763 substantially less calcite growth, calcium is deposited on the surface of the eggshell membrane  
764 and, in the case of gekkonids and the tuatara, crystal growth proceeds inward toward the center  
765 (Choi et al., 2018). The strikingly divergent structure and directionality of eggshell formation  
766 between Archelosauria and Lepidosauria suggests that the dissimilar processes of eggshell  
767 formation are a result of genetic drift (e.g. Schiffman & Ralph, 2022), selection for specific  
768 eggshell traits, or, in the case of an early origin of viviparity in Amniotes (Jiang et al., 2023)  
769 and/or Lepidosauria (Pyron & Burbrink, 2014), eggshells are a derived convergent trait.

770 Hypothetically, if a version of the avian eggshell was the microstructure for basal  
771 Lepidosauria, loss of mammillary knobs and their basal caps should have prevented calcium  
772 deposition since mammillary knobs are the site at which calcium carbonate spontaneously  
773 precipitates into calcite in Archelosaurs. Given that embryonic signaling supports at least two  
774 main differences between oviparous and viviparous squamates—the timing of calcium secretions  
775 and the length of embryonic retention (Griffith et al., 2015, 2017; Stewart & Ecy, 2010)—the  
776 loss of mammillary knobs/basal caps may have supported an early origin of viviparity in  
777 squamates. It would have theoretically facilitated 1) an early loss of the eggshell, 2) enhanced  
778 contact between maternal and embryonic tissues and 3) enhanced signaling from the embryo to  
779 support both altered timing of calcium secretions and hormonal signaling for extended  
780 embryonic retention. This potential mechanism for an early origin of viviparity in squamates is  
781 proposed here, for the first time, as the basal cap hypothesis. When mammillary knobs originated  
782 is of paramount importance to the basal cap hypothesis, and inferences that can be gained from  
783 applying it to the evolution of oviparity and viviparity in amniotes. If a version of the avian  
784 eggshell was the ancestral microstructure of oviparous amniotes, the loss of basal caps could

785 result in a rapid loss of the eggshell and thus a relatively fast transition to viviparity or extended  
786 embryonic retention.

787       Extending to the ancestral state of amniotes (e.g. Jiang et al., 2023; Laurin, 2005; Romero,  
788 1957), absence of functional “mammillan” with P-FCD in squamates and mammals would be  
789 consistent with a derived state of calcified eggshells in Archelosaurs. Absence of functional  
790 “mammillan” with P-FCD exclusively in Lepidosaurians would be consistent with the basal cap  
791 hypothesis. Presence of functional “mammillan” with P-FCD across Amniota would be  
792 consistent with the conventional understanding that the amniote egg evolved to prevent  
793 desiccation and enable gas exchange following oviposition of eggs on land (Romero, 1957).  
794 Overall, identifying the evolutionary trajectories of the biosynthetic pathway of “mammillan”  
795 across amniotes is likely to create a better picture of the evolution of the amniote egg.

796       New recommendations for estimating ancestral microstructure of amniote eggshells have  
797 recently been put forth, which abandons the traditional classification of hard/soft/semi-rigid  
798 shells (Legendre et al., 2022). Including the structure of eggshell membranes in viviparous  
799 squamates (e.g. Corso et al., 2000) would also improve phylogenetic reconstructions of the  
800 amniote eggshell.

801       Several pieces of biological evidence lend themselves to an early origin of viviparity in  
802 Lepidosaurians and the basal cap hypothesis including—the lack of homology between the semi-  
803 rigid shells of testudines and Lepidosaurians (Legendre et al., 2022), the later stage of embryonic  
804 development when eggs are commonly oviposited in squamates (Blackburn, 1995), and the more  
805 predominant reliance on yolk calcium rather than eggshell calcium in squamates compared to  
806 Archelosaurs (Packard, 1994; Stewart & Ecyay 2010). Viviparity in the most recent common  
807 ancestor of Lepidosaurians may provide clear evolutionary insights on these phenomena.

808 Other features of eggshells are also worth consideration. In chickens, ovotransferrin is  
809 present in the eggshell membrane and basal cap-layer (Gautron, Hincke, Panhéleux et al., 2001).  
810 Ovotransferrin promotes the development of elongated crystals (Gautron, Hincke, Panhéleux et  
811 al., 2001). The resulting shell matrix is made up of the crystal layer and cuticle (Hamilton, 1986).  
812 On the inner portion of the avian eggshell, it is unclear what prevents growing crystalized cones  
813 from extending into the inner membrane or the albumen. Collagen type X has been implicated  
814 (Arias et al., 1993, 1997; Hincke et al., 2012). The role of collagen type X in creating a boundary  
815 that prevents calcite from passing through the eggshell membrane could inform squamate  
816 eggshells deposition (as discussed, they deposit calcium only on the outer surface, or crystals  
817 grow inward). The only non-avian eggshell matrix protein, pelovaterin, was identified in the soft-  
818 shell turtle (Lakshminarayanan et al., 2005).

819 Over 500 proteins are found in the chicken eggshell matrix (Mann, Maček, & Olsen, 2006;  
820 Mikšík et al., 2007, 2010). Ovocleidin-116 (*OC-116*), ovocalyxin-36 (*OCX-36* or *BPIFB4*),  
821 ovocalyxin-21 (*OCX-21*), and ovocleidin-17 (*OC-17*) are important for avian eggshell formation  
822 (Hernández-Hernández, Gomez-Morales et al., 2008; Jonchère et al., 2010; Tian et al., 2010).  
823 *OC-116*, *OC-36*, *OCX-21*, and *OC-17* are some of the most differentially expressed genes during  
824 eggshell calcification in chickens (Gautron et al., 2007; Hincke et al., 1999, 2012; Jonchère et al.,  
825 2010). Ovocalyxin-21 may serve as a chaperone protein along with the protein endoplasmic  
826 (ENPL) to facilitate proper folding of the avian eggshell matrix (Jonchère et al., 2010). In birds,  
827 *OC-17* is concentrated in the inner mammillary cone layer, it interacts strongly with ACC, and it  
828 is implicated in early stages of biomineralization of the eggshell (Gautron et al., 2021).

829 Originally considered avian-specific, several homologs of avian eggshell matrix proteins  
830 have now been identified in non-avian reptiles and mammals (Le Roy et al., 2021). A recent



831 study found a significantly reduced number of intact avian eggshell matrix proteins in viviparous  
832 squamates compared to oviparous squamates, a pattern that was especially apparent in snakes  
833 (Xie et al., 2022). This study also found that *OC-17* was only absent in viviparous squamates but  
834 was always present in the oviparous species in the dataset (Xie et al., 2022). Due to this, and the  
835 central role of *OC-17* in avian eggshell formation in birds, they ascribe losing intact *OC17* with  
836 the prevention of reversals back to oviparity (Xie et al., 2022). However, given that *OC-17* is  
837 implicated in initiation of mineralization in the mammillary cone layer, which is absent in  
838 squamates, the necessity of *OC-17* for squamates eggshell formation requires further  
839 investigation. Other genes, like osteopontin (*OPN* or *SPPI*), also play a central role in  
840 biomineralization of the avian eggshell and should be investigated in squamates.

841 *OCX-36* and other bactericidal/permeability-increasing (BPI) family B proteins (also called  
842 *LPLUNCs*) are now thought to have a common origin in vertebrates with multiple duplication  
843 events (Gautron et al., 2007; Tian et al., 2010). Orthologs of *OCX-36* are found in Archelosauria  
844 and Monotremata (Le Roy et al., 2021). In birds, *OCX-36* plays a role in innate immune  
845 responses and is found in high concentrations in the inner eggshell membrane (Gautron et al.,  
846 2007, 2011; Tian et al., 2010).

847 *OC-116* is homologous to mammalian *MEPE*, which plays a role in bone and teeth  
848 mineralization (Bardet et al., 2010a, 2010b). In birds, *OC-116* influences shell thickness, elastic  
849 modulus, and egg shape (Le Roy et al., 2021). *OC-116* was identified in a crocodile, *Crocodylus*  
850 *siamensis*, proteome (Le Roy et al., 2021; Mikšík et al., 2018). Synteny analysis across seven  
851 turtle species and platypus (*Ornithorhynchus anatinus*) revealed absence of *MEPE/OC116* (Le  
852 Roy et al., 2021). Other genes and lncRNAs are purported to be important for the quality of  
853 eggshell formation in hens—*FGF14*, *COL25A1*, *GPX8*, and several members of the solute

854 carrier protein (*SLC*) gene family (Yang et al., 2020). Research into lncRNAs activity in  
855 squamate reproductive tissues during embryonic development represents another valuable track  
856 for research.

857 Various evolutionary genomics studies have revealed squamate-specific candidates for shell  
858 formation (e.g. Recknagel et al., 2021a; Gao et al., 2020). Some of these candidates span the  
859 major clades of amniotes. Seven of the genes expressed during eggshell gland development in  
860 *Phrynocephalus przewalskii*—*HYPOUI*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*, *RRBP1* and  
861 *TRAMI*—are purported to be important for eggshell calcification in chickens (Brionne et al.,  
862 2014). Given this overlap across species that diverged over 300 million years ago (Shen et al.,  
863 2011), these are excellent candidates for further exploration.

864 A functional genomics study harnessed hybridizations of oviparous and viviparous  
865 individuals of *Zootoca vivipara* to reveal 17 SNPs and 38 genes associated with eggshell traits  
866 (Recknagel et al., 2021a). These genes enriched terms related to cell communication and the  
867 immune system, while differentially expressed gene during gravidity enriched pathways for  
868 transforming growth factor (Recknagel et al., 2021a). The three loci with the strongest  
869 association with eggshell traits mapped closely to *LG MN*, *LYPLA1*, and *CRTCI* (Recknagel et  
870 al., 2021a). The association of these genes with eggshell traits is particularly interesting. *LG MN*,  
871 for example, is involved with the cadherin pathway. Cadherins have an established role in  
872 squamate reproduction. In squamates, previous literature discusses how cadherins influence  
873 embryonic attachment in viviparous taxa (Wu et al., 2011). *LG MN* is also differentially  
874 expressed across many viviparous squamates and mammals (Recknagel et al., 2021a). Thus,  
875 *LG MN*, appears to support both oviparous and viviparous gestation in different ways. There are a  
876 number of ways to approach exploring how *LG MN* may support both maternal-fetal

877 interconnectivity (viviparous individuals) and eggshell formation (oviparous individuals). Cell-  
878 to-cell communication analysis using single cell data on uteruses of a reproductively bimodal  
879 species would enable researchers to identify different interaction networks of *LGMN* and  
880 associated cells in oviparous vs viviparous individuals.

881 During gravidity in *Saiphos equalis* two GO terms associated with calcium homeostasis are  
882 enriched by the set of upregulated genes (Foster et al., 2020). However, most of these genes are  
883 associated with regular cellular responses to calcium and even those associated with calcium  
884 transport are upregulated in both early and late stages of gravidity (Foster et al., 2020). Their role  
885 in eggshell formation in this uniquely labile species is therefore ambiguous.

886 In oviparous individuals of another reproductively bimodal skink, *Lerista bougainvillii*, only  
887 two genes are significantly differentially expressed in the gravid uterine tissue compared to non-  
888 gravid uterine tissue (Griffith et al., 2016). No genes are differentially expressed in the gravid  
889 uterine tissue of the oviparous garden skink, *Lampropholis guichenoti*, compared to non-gravid  
890 uterine tissue (Griffith et al., 2016). The genes involved in the shelling process in these species  
891 may not involve changes in expression from the non-gravid state. The dissimilarity in uterine  
892 gene expression profiles across lizards during gravidity suggests there may be multiple ways  
893 oviparous squamates shell their eggs. Given the variation already observed, the eggshell  
894 deposition in squamates should be considered in a phylogenetic context and under the different  
895 evolutionary history inferred by ancestral state reconstructions (Harrington & Reeder, 2017;  
896 Pyron & Burbrink, 2014). Supplementary table 1 compares candidate genes associated with  
897 eggshell formation and shell gland development in squamates to that of birds.

898

899 (4) *Pleiotropy of genes and proteins involved with eggshell formation*

900 Substantial pleiotropy of genes involved with eggshell formation would imply that regardless  
901 of parity mode, taxa have innately conserved toolkits that can be readily exploited to form an  
902 eggshell for oviparous gestation. In addition to the candidate genes associated with both  
903 gestation length and eggshell traits in *Zootoca vivipara* (Reckagel et al., 2021a), several genes  
904 associated with eggshell deposition have pleiotropic effects within species or have different  
905 effects in oviparous vs. viviparous amniotes. Osteopontin (*SPP1* or *OPN*) is found in bone and  
906 kidneys, and transports calcium to other tissues in the body (Pines et al., 1995). It plays an  
907 important role in calcium carbonate biomineralization of the avian eggshell (Gautron et al.,  
908 2021). It is highly expressed in the chicken uterus during calcification (Jonchère et al., 2010) but  
909 supports pregnancy recognition and implantation in sheep (Bazer et al., 2011). Improper  
910 functioning of *SPP1* in the uterus leads to cracked and abnormal shells in birds (Arazi et al.,  
911 2009; Hincke et al., 2008).

912 When expressed in the uterus, some bone morphogenic protein-coding genes (*BMPs*) aid  
913 eggshell calcification (Jonchère et al., 2010). *BMPs* are part of the *TGF- $\beta$*  superfamily and are  
914 involved with the formation of new cartilage and bone, and with biomineralization in corals and  
915 mollusks (Canalis et al., 2003; Lelong et al., 2000; Zoccola et al., 2009). Chordin (*CHRD*) is an  
916 antagonist of the *BMP* pathway. *BMP*-binding endothelial regulatory protein (*BMPER*) and  
917 *CHRD* are expressed in the chicken uterus during the stage of eggshell calcification (Jonchère et  
918 al. 2010). Regulation of *BMPs* by *CHRD* is essential for early embryogenesis and adult  
919 homoeostasis.

920 *BMPER* and seven *BMPs* are expressed during gestation in *Chalcides ocellatus*, a viviparous  
921 skink (Brandley et al., 2012). Most of these are upregulated (Brandley et al. 2012). *BMP* genes  
922 are expressed during both gravidity and non-gravidity in oviparous *Lerista bougainvillii* and

923 *Lampropholis guichenoti* (Griffith et al., 2016). *BMP2* is upregulated in oviparous late gestation  
924 compared to viviparous late gestation in the reproductively bimodal lizard, *Saiphos equalis*  
925 (Foster et al., 2020).

926 Differential expression of *BMPR1B* is associated with differences in eggshell quality in  
927 chickens (Yang et al., 2020). Another study associated stage-specific high-expression of  
928 *BMPR1B* with the stage corresponding to extended embryonic retention and placentation in  
929 *Phrynocephalus vlangalii* (Gao et al., 2019). They identified a co-expression network of highly  
930 expressed genes, including *BMPR1B*, that they associated with placentation (Gao et al., 2019).  
931 *BMPR1B* also reaches significant levels of differential expression in uterine tissues of other  
932 gestating viviparous lizards, *Chalcides ocellatus* and *Pseudemoia entrecasteauxii*, compared to  
933 non-gestational uterine tissue (Brandley et al., 2012; Griffith et al., 2016). Receptors for *BMPs*  
934 are also expressed in the uterus during gestation in other viviparous lizards, *Phrynocephalus*  
935 *vlangalii* and *Pseudemoia entrecasteauxii* (Gao et al., 2019; Griffith et al., 2016). Perhaps  
936 unsurprisingly, *BMPR1B* is also differentially expressed in the uterus of viviparous *Zootoca*  
937 *vivipara* compared to oviparous individuals during gestation.

938 The potential role of these genes in squamate eggshell formation remains unclear. *BMPs*  
939 influence on dorsal-ventral axis patterning during early embryogenesis and growth of skeletal  
940 structures in post-natal tissues (Medeiros & Crump, 2012). It may be difficult to disentangle their  
941 roles in embryonic development, placental development, and eggshell deposition. Future  
942 research on them may inform scientific understanding of parity mode evolution.

943 *SLIT* genes are purported to be involved with folding the eggshell matrix in chickens  
944 (Jonchère et al., 2010). The *SLIT2* gene functions across birds and mammals in diverse organs,  
945 and encodes a protein that provides a structural framework for protein-protein interactions

946 (Jonchère et al., 2010; Marillat et al., 2002). In a functional genomics study, *SLIT2* was  
947 identified as an important gene for eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).  
948 *SLIT2* is among the 50 most downregulated genes in the uterus during pregnancy in the  
949 viviparous African ocellated skink, *Chalcides ocellatus*, compared to non-pregnancy (Brandley  
950 et al., 2012). However, in the uterus of the yolk-sac placenta in the viviparous skink, *Pseudemoia*  
951 *entrecasteauxii*, *SLIT2* is upregulated compared to non-reproductive uterine tissue (Griffith et al.,  
952 2016). *SLIT3* is differentially expressed during the stage of placentation in the viviparous agama  
953 lizard, *Phrynocephalus vlangalii* (Gao et al., 2019). *SLIT* genes also play a role in axonal  
954 pathfinding and neuronal migration in rats (Marillat et al., 2002). *SLIT2* was associated with  
955 reproduction in humans (Chen, Chu et al., 2015).

956 Podocalyxin (*PODXL*) is a sialoprotein associated with eggshell calcification in chickens  
957 (Jonchère et al., 2010). In the viviparous Qinghai toad-headed agama lizard, *Phrynocephalus*  
958 *vlangalii*, a weighted gene correlation network analysis associated *PODXL* with uterine  
959 structural changes (Gao et al., 2019). The gene may play a role in placentation in these species  
960 given that it was also differentially expressed in the uterus during the stage of placentation (Gao  
961 et al., 2019). Interestingly, *PODXL* is downregulated in the uterus of the yolk-sac placenta in  
962 another viviparous skink, *Pseudemoia entrecasteauxii* (Griffith et al., 2016). Based on its role in  
963 chickens and *P. vlangalii*, *PODXL* is a good candidate for further research on the molecular  
964 evolution of eggshell formation and placentation in squamates.

965

#### 966 (5) Eggshell formation termination

967 When eggshell formation is terminated, the egg is still bathed in the supersaturated  
968 calcium and bicarbonate ion fluid (Hincke et al., 2012). Some component(s) of the terminal

969 uterine fluid may prevent precipitation of calcium carbonate (Gautron, Hincke & Nys, 1997),  
970 such as phosphate anions (Lin & Singer, 2005). The presence of phosphorous in the superficial  
971 layers of the chicken shell suggest it may be a factor preventing the deposition of calcite crystals  
972 in the terminal stage. Additionally, the high concentration of *OCX-32* in the outer eggshell and  
973 cuticle, suggest that the gene may inhibit proteinaceous crystal growth in the terminal stage of  
974 eggshell calcification (Gautron, Hincke, Mann et al., 2001). It is informative to viviparous  
975 reproduction and consistent with the basal cap hypothesis that exposure to precursors of the  
976 eggshell does not necessitate eggshell deposition. The influence of phosphate anions and *OCX-*  
977 *32* on inhibition of calcium carbonate precipitation on the eggshell membrane of viviparous  
978 squamate embryos has not been examined to my knowledge.

979

#### 980 *(6) Rotating the egg for eggshell formation*

981 Oviparous amniotes rotate the egg for calcium formation and viviparous mammals rotate the  
982 embryos for parturition. One hurdle to reversing back to oviparity may be re-evolving rotation of  
983 the egg for shell formation early in gravidity (Griffith et al., 2015). Given the complex  
984 musculature of the uterus across taxa, that allows for multidirectional force for parturition and  
985 eggshell formation, it is difficult to determine the degree of difficulty for re-evolving appropriate  
986 timing of egg-rotation. Cadherins and hormonal signaling support embryonic attachment (Wu et  
987 al., 2011; Biazik et al., 2012), which can prevent rotation of the egg. Oviparous taxa lack  
988 embryonic attachment, enabling the uterus to rotate the egg for eggshell formation. This rotation  
989 does not happen until later in gestation for eutherian mammals when, for example, the embryo  
990 detaches and cadherins become less concentrated (Wu et al., 2011). Perhaps a candidate gene for  
991 studying this is, a cadherin *CDH5*, the only gene that is differentially expressed in all viviparous

992 squamates studied thus far studied (Recknagel et al., 2021a). Genes that enrich the GO term for  
993 “voltage-gated calcium channel activity” are also useful candidates for investigating uterine  
994 rotation associated with eggshell formation because voltage-gated calcium channels effect the  
995 action potential of cells and can cause muscle contractions.

996

997 (7) Discussion & future directions—eggshell formation and parity mode evolution

998 The process of eggshell formation is more resolved in birds compared to non-avian reptiles  
999 and monotremes (Choi et al., 2018; Frankenberg & Renfree 2018). I described some overlaps  
1000 gleaned from the literature which prove as curious candidates for further research  
1001 (Supplementary Table 1). Of particular interest are avian eggshell matrix proteins (Alföldi et al.,  
1002 2011; Le Roy et al., 2021; Tian et al., 2010; Xie et al., 2022), genes with biomineralizations  
1003 functions, candidate genes associated with eggshell traits in *Zootoca vivipara* (Recknagel et al.,  
1004 2021a), and the homologs for avian eggshell matrix proteins identified in the *Anolis carolinensis*  
1005 genome (Alföldi et al., 2011; Tian et al., 2010). Additionally, genes purported to be important for  
1006 eggshell calcification in chickens associated with eggshell gland formation in an oviparous  
1007 lizard, *Phrynocephalus przewalskii*, are relevant—*HYPOUI*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*,  
1008 *RRBP1* and *TRAMI* (Brionne et al., 2014; Gao et al., 2019). Overlaps between the genes  
1009 associated with gestation length and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a)  
1010 hint at genes that could potentially evolve to innately effect multiple traits relevant to parity  
1011 mode transitions. The basal cap hypothesis also offers a simple evolutionary mechanism to  
1012 investigate the evolutionary history of amniote parity mode evolution (see section III.3).  
1013 Alternatives to the basal cap hypothesis are that dissimilar eggshells and eggshell deposition



1014 processes evolved through selective pressure, genetic drift, or both. Fortunately, the basal cap  
1015 hypothesis can be utilized to ascertain the likelihood of this.

1016

#### 1017 **IV. Placentation & Transport of Embryonic Water, Gas, and Nutrients**

1018

1019 The evolutionary pressures on fluid allocation, gas exchange and nutrient transport should  
1020 differ between oviparous and viviparous taxa because their sources of all or some of these  
1021 resources differ (Blackburn, 1992; Bonnet et al., 2001; Bonnet, Naulleau & Shine, 2017; van  
1022 Dyke et al., 2014). In viviparity, maternal gas and water are accessed through the chorioallantois,  
1023 which is especially important in the latter half of development (van Dyke et al., 2014; Carter,  
1024 2012). Nutrients can be available from the yolk, maternal transfer, or both yolk and maternal  
1025 transfer.

1026 While viviparity is associated with shared patterns of uterine gene expression during amniote  
1027 gestation (Recknagel et al., 2021a), the same does not occur in viviparous amniote placentas  
1028 (Foster et al., 2022). Instead, different genes that serve similar functions are recruited to the  
1029 placenta across independent origins of viviparity (Foster et al., 2022). Additionally, where other  
1030 amniotes can rely on the albumen for fluid allocation, squamates lack an albumen (Blackburn &  
1031 Stewart, 2021). The eggshells of various squamates supports uptake of water from the  
1032 environment (Blackburn & Stewart, 2021). The evolutionary implications of this have not been  
1033 documented to my knowledge.

1034

1035 *(1) Anatomy & methods of water, gas & nutrient provisioning*

1036 The embryonic membranes regulate embryonic fluid transport, nutrient supply, respiration,  
1037 immunity, and waste (Brace, 1997; Burton & Tullett, 1985; Ferner & Mess, 2011; Packard &  
1038 Packard, 1980). Fluids are important for the developing embryo because they prevent desiccation  
1039 and compression (Ferner & Mess, 2011; Packard & Packard, 1980). Over-abundance or under  
1040 abundance of embryonic sac fluids leads to reproductive failure (Chamberlain et al., 1984;  
1041 Fedakâr et al., 2016; Hadi, Hodson & Strickland, 1994; Mercer et al., 1984). Water is the  
1042 predominant resource provisioned from the mother in most viviparous squamates (Lourdais et  
1043 al., 2015).

1044 Oxygen flux in embryonic mammals is largely determined by oxygen-diffusing capacity of  
1045 the placenta, the rates of blood flow in the umbilical and uterine arteries, and the oxygen  
1046 capacities and affinities of fetal and maternal blood (Carter, 2009). Reptilian and mammalian  
1047 blood vessels differ in basic characteristics such as capillary density, capillary surface, and  
1048 oxygen diffusion gradients (Pough, 1980). Oviparous taxa regulate gas exchange through pores  
1049 in their eggshells.

1050 Patterns of embryonic nutrient exchange can be broadly categorized into lecithotrophy,  
1051 obtaining nutrients from the yolk, and placentrophy or matrotrophy, obtaining nutrients from the  
1052 mother. Taxa belonging to Archelosauridae are lecithotrophic. The ancestral state of mammals  
1053 was most likely oviparous matrotrophy that later evolved into viviparous matrotrophy in therians  
1054 (Blackburn, 2005). The ancestral state of reptiles was likely lecithotrophy (Blackburn, 2005).  
1055 Most viviparous squamates are lecithotrophic, some are lecithotrophic and matrotrophic, and a  
1056 few have specializations for substantial matrotrophy (e.g. Blackburn, 2015a, Blackburn, 1985b;  
1057 Stewart & Thompson, 1993; Thompson, Stewart et al., 1999; van Dyke et al., 2014). Even in  
1058 lecithotrophic viviparous squamates some degree of organic or inorganic nutrients pass through

1059 the chorioallantoic placenta (Blackburn, 2005; Swain & Jones, 1997, 2000; Stewart & Eday,  
1060 2010; Thompson, Stewart et al., 1999; Thompson & Speake, 2002). Reversals may be most  
1061 unlikely in lineages that have specialized placentas for substantial nutrient exchange because  
1062 they would need to re-evolve lecithotrophy. Highly matrotrophic squamates are extremely rare  
1063 (Blackburn, 2015a).

1064

1065 *(2) Evolutionary history of yolk-sac formation and yolk processing*

1066 Vitellogenesis is the process of yolk formation in the oocyte, providing the embryo with a  
1067 valuable source of nutrients, primarily through the accumulation of precursor proteins to yolk,  
1068 vitellogenins. Vitellogenin is produced in the liver, called hepatic vitellogenesis, and transported  
1069 to the maturing ovum (Ho, 1987). Vitellogenins were lost in all mammals except monotremes  
1070 (Brawand, Wahli & Kaessmann, 2008). They are a primary source of nutrition for other  
1071 amniotes. Functionally similar to vitellogenin, caseins have persisted in all mammalian milks  
1072 (Brawand et al., 2008). Active functioning of the yolk sac is restricted to the first trimester in  
1073 placental mammals, and it is postulated to provide nutrients to the embryo (Kuzima et al., 2023).  
1074 The detection of glycodelin in the yolk sac epithelium also supports this (Burton et al., 2002). In  
1075 the yolk-sac of bats, dogs, and non-human primates the mesoderm derived layer is absorptive  
1076 and may transfer substances from the exocoelomic cavity where the yolk sac is located (Enders  
1077 et al., 1976; Freyer & Renfree, 2009; King & Wilson, 1983; Lee et al., 1983).

1078 The morphology of the yolk-sac and process of vitellogenesis differs between birds and non-  
1079 avian reptiles. In birds, during the process of meroblastic cleavage, the zygote's cells divide  
1080 while the yolk component does not. The yolk forms a large, fluid, non-cellularized mass  
1081 surrounded by the extraembryonic yolk sac. The formation of the yolk-sac placenta in birds has

1082 the following pattern—first the bilaminar omphalopleure forms and then trilaminar  
1083 omphalopleure; blood vessels move into folds of the extraembryonic endoderm, becoming  
1084 stratified epithelium; the folds carrying the blood vessels reach the peripheral regions of the yolk  
1085 only and the center of the yolk mass remains uncellularized (Starck, 2021). Intensive  
1086 development of hemopoietic tissue surrounding the blood vessels during most of embryonic  
1087 development, thus far, appears to be unique to birds (Starck, 2021). Compared to non-avian  
1088 sauropsids, the unique pattern of yolk processing in birds facilitates faster embryonic  
1089 development (Blackburn, 2021).

1090 The yolk sac characteristic of non-avian reptilian eggs serves as a model for the transition  
1091 between the egg of anamniotes and amniotes (Blackburn, 2020). A series of recent papers,  
1092 covering species of snakes, lizards, crocodiles, and turtles, indicate that these taxa utilize similar  
1093 developmental pathways of yolk-sac formation and yolk processing that differs from birds  
1094 (Blackburn, 2020, 2021; Blackburn et al., 2019; Elinson et al., 2014; Elinson & Stewart 2014;  
1095 Stinnett et al., 2011). Across these taxa, a bilaminar/trilaminar omphalopleure overgrows the  
1096 yolk mass, and the yolk mass gets invaded by proliferating endodermal cells that phagocytose  
1097 the yolk material. These cells form clumps, progressively filling the yolk mass. Small blood  
1098 vessels derived from yolk sac vasculature invade the yolk sac cavity and the endodermal cells  
1099 arrange in monolayers around these vessels, forming “spaghetti bands” (Blackburn, 2021). The  
1100 yolk sac of *Pantherophis guttatus* is one suitable model for studying the transition of the yolk-  
1101 sac from anamniotes to amniotes (Elinson & Stewart, 2014; Elinson et al., 2014).

1102 A major difference between non-avian reptilian yolk-sac formation is the morphology and  
1103 extent of vascularization and cellularization in the yolk sac cavity (Starck, 2021). Birds have a  
1104 yolk-sac with absorptive endodermal lining that digests nutrients and send them into blood

1105 circulation (Starck, 2021) whereas snakes, lizards, turtles, and crocodylians have a yolk sac that  
1106 becomes invaded by endodermal cells that proliferate and phagocytose yolk material (Blackburn,  
1107 2021). In these taxa, yolk material becomes cellularized, digested, and transported by vitelline  
1108 vessels to the developing embryo (Blackburn, 2021). Factors involved with cellularization of the  
1109 yolk-sac are proposed to include cell cycle regulators and structural proteins (Elinson et al.,  
1110 2014). Generation of these cells are suspected to be reliant on processes of angiogenesis and are  
1111 likely transcriptionally active (Elinson et al., 2014). Few transcriptomic profiles of yolk-sac  
1112 placentas in reptiles have been documented to my knowledge (Griffith et al., 2016). Significant  
1113 overlaps in the yolk-sac transcriptomes of human, mice, and chicken—including apolipoproteins  
1114 and SLC transporters—however, suggest functional conservation (Cindrova-Davies et al., 2017).

1115 As discussed in a previous section, progesterone inhibits myometrial contractility, but it also  
1116 inhibits estrogen-induced hepatic vitellogenin synthesis (Custodia-Lora, Novillo, & Callard,  
1117 2004; Callard et al., 1992). Variable progesterone concentrations in circulation throughout  
1118 gestation in viviparous squamates may reflect a trade-off to allow estrogen expression to support  
1119 hepatic vitellogenin synthesis during embryonic development, thus supporting nutrient  
1120 provisioning during the lengthened embryonic retention. Although hepatic vitellogenesis usually  
1121 ceases during gestation, vitellogenin synthesis and mother-to-embryo transfer was detected in  
1122 one viviparous fish, *Xenotoca eiseni*, during gestation (Iida et al., 2019). Future research should  
1123 consider the timing of vitellogenin synthesis throughout the reproductive cycle in gestating and  
1124 non-gestating viviparous squamates to investigate this further.

1125

1126 (3) *Evolutionary history of placentrophy in mammals & squamates*

1127 Traditionally, it was thought that placentrophy evolved after viviparity in squamates  
1128 (Packard, Tracy, & Roth, 1977; Shine & Bull, 1979). Further research demonstrated that  
1129 placentrophy and viviparity evolved simultaneously (incipient matrotrophy) in mammals and  
1130 may have in squamates (Blackburn, 1985, 1992, 2005, 2006; Stewart & Eday, 2010). The  
1131 incipient matrotrophy model relies on evidence that 1) uterine provisioning of nutrients predates  
1132 the origin of viviparity (Blackburn 1985, 1992, 2006), 2) uterine and embryonic tissues have a  
1133 close anatomical and physiological association in viviparous taxa and 3) some degree of  
1134 placental transfer of organic or inorganic molecules occurs in viviparous taxa (Stewart & Eday,  
1135 2010). In squamates, the potential for both incipient matrotrophy and evolution of placentrophy  
1136 after viviparity is supported (Stewart & Eday, 2010). Facultative placental nutrient provisioning  
1137 and incipient matrotrophy may have driven the evolution of squamates with substantial  
1138 matrotrophic nutrient provisioning (Stewart, 2020; Swain & Jones, 2000).

1139 Placentation and implantation are not homologous in mammals compared to squamates  
1140 (Griffith, van Dyke & Thompson, 2013). Several placental specializations for gas and nutrient  
1141 exchange are unique to mammals including erosion of the uterine mucosa, extensively invasive  
1142 implantation, hemochorial contact, retention of a vascularized choriovitelline membrane, and  
1143 countercurrent patterns of blood flow (Blackburn, 2005). This enables extensive exchange of  
1144 nutrients in addition to water and gas. The vast majority of viviparous squamates have the most  
1145 superficial type of chorioallantoic placenta called epitheliochorial placenta (Blackburn, 1993).

1146 Nutrient provisioning through placentrophy is obligate for embryonic development in only  
1147 five lineages of squamates, all of which are scincid lizards (Blackburn, 2000; Flemming &  
1148 Blackburn, 2003; Ramírez-Pinilla et al., 2011; van Dyke et al., 2014). *Pseudemoia*  
1149 *pagenstecheri*, a lizard with a highly specialized placenta, out-performs lecithotrophic oviparous

1150 close relatives in the relative amount of nutrients it transfers to the embryo (Stewart et al., 2009).  
1151 *Pseudemoia entrecasteauxii* is a moderately matrotrophic viviparous skink, with roughly half of  
1152 embryonic nutrient uptake from the yolk and half through a specialized cyto-epitheliochorial  
1153 placenta (Adams et al., 2005; Speake et al., 2004; Stewart & Thompson, 1993, 2009).

1154 Specializations of the chorioallantoic placenta for nutrient provisioning in some squamates  
1155 include elaborate specializations for uterine secretion and absorption, including placentomes,  
1156 chorionic areolae, hypertrophied uterine mucosa, and chorionic epithelia modified for absorption  
1157 (Blackburn, 2005). In squamates, specializations for gas exchange across the chorioallantoic  
1158 placenta include decreased diffusion distance between maternal and fetal capillaries, uterine  
1159 vascularity, shell membrane deterioration, and modifications of both fetal and maternal blood  
1160 properties (Blackburn, 1998, 2005; Blackburn & Lorenz, 2003; Blackburn & Vitt, 2002).

1161 Mammalian placenta-specific genes have deep origins in vertebrates (Rawn & Cross, 2008).  
1162 Placentation to support viviparity likely employs genes that are ancestral to the chorioallantois.  
1163 However, one study that looked at placentation and gene expression across a small sample of  
1164 divergent amniotes found only one gene with a placentrophy-specific pattern of gene expression,  
1165 *DIO3* (Griffith, Brandley et al., 2017). In mammals, *DIO3* is an imprinted gene and  
1166 preferentially paternally expressed. The authors suggest that the gene may increase offspring  
1167 resource uptake during pregnancy in the horse and a viviparous lizard, *Pseudemoia*  
1168 *entrecasteauxii*, where it is recruited to the placenta (Griffith, Brandley et al., 2017).

1169

#### 1170 (4) Genes involved with embryonic water, gas, and nutrient transport

1171 Water transport in animals is regulated by a family of molecular water channels called  
1172 aquaporins (AQs or AQPs) (Borgnia et al., 1999). In humans, *AQP1*, *AQP3*, *AQP4*, *AQP8* and

1173 *AQP9* are found in the placenta but further research is needed to understand how these influence  
1174 water fluxes between maternal and fetal tissues (Damiano, 2011). Transcriptomic analysis on  
1175 uterine tissue of the gestating, viviparous skink, *Chalcides ocellatus*, reveal differential  
1176 expression of *AQP1*, *AQP3*, *AQP5*, *AQP6*, *AQP8*, *AQP9* and *AQP11* when compared to non-  
1177 gestating uteruses (Brandley et al., 2012). In birds, *AQP1* is expressed in the chorioallantoic  
1178 membrane, and it is suggested to influence angiogenesis throughout embryonic development  
1179 (Ribatti et al., 2002). In a viviparous lizard, *Pseudemoia entrecasteauxii*, *AQP8* and *AQP9* were  
1180 more highly expressed in the chorioallantoic placenta compared to the yolk-sac placenta (Griffith  
1181 et al., 2016). During gestation in both oviparous and viviparous populations of the reproductively  
1182 bimodal skink, *Saiphos equalis*, several genes involved with water homeostasis are upregulated  
1183 in the uterus including *AQP1*, *AQP3* and *AQP12B* (Foster et al., 2020). In uteruses of *Saiphos*  
1184 *equalis*, *AQP5* and *AQP8* are upregulated during oviparous late gestation compared to viviparous  
1185 late gestation. In sheep, *AQP3* is differentially expressed during gestation, where it serves a dual  
1186 role of water transport to the embryo and fetal urea export (Johnston et al., 2000). This is similar  
1187 to the function of *AQP9* in humans (Damiano, 2011). Immunocytochemistry reveals that *AQP1*  
1188 and *AQP3* are expressed in the uterus of the highly placentrophic South American scincid lizard,  
1189 *Mabuya sp.* (Wooding et al., 2010). In *Zootoca vivipara*, *AQP9* is upregulated at midgestation  
1190 (Recknagel et al., 2021a).

1191 Some molecules are implicated in the regulation of aquaporins including insulin (INS),  
1192 human chorionic gonadotropin (HcG), cyclic adenosine monophosphate (cAMP) and cystic  
1193 fibrosis transmembrane conductance regulator (CFTR) (Damiano, 2011). Genes predicted to be  
1194 involved with reproduction in *Anolis carolinensis* are enriched for the GO term for cAMP-  
1195 mediated signaling (Alföldi, Di Palma, et al., 2011). Further comparative research should be



1196 done to elucidate the functional differences of aquaporins in oviparous and viviparous amniotes  
1197 and how they relate to the differing conditions under which these embryos develop.

1198 Genes involved embryonic oxygen transport precede the origin of amniotes. Hemoproteins  
1199 arose in evolutionary history well before they were used for placental oxygen transfer (Hardison  
1200 1998). In mammals, adult (Alpha: HBA; Beta: HBB, HBD) and embryonic hemoglobins (Alpha:  
1201 HBZ, HBA; Beta: HBE, HBG, and HBH) are involved with oxygen transport (Carter, 2012).  
1202 Some of these are unique to eutherian mammals following a series of duplication events (Opazo  
1203 et al., 2008). However, fetal hemoglobins are found in turtles, lizards, and snakes (Pough, 1980).  
1204 HBA, HBB and HBM are all significantly downregulated in the uterine tissue of the viviparous  
1205 African Ocellated Skink, *Chalcides ocellatus*, during gestation compared to non-gestation  
1206 (Brandley et al., 2012). The oxygen demands of reptile embryos are relatively low until stage 30,  
1207 when most oviparous taxa oviposit (Shine & Thompson, 2006). In viviparous and oviparous  
1208 species with long egg retention, embryonic demand for maternal provision of oxygen and  
1209 removal of CO<sub>2</sub> increases at this stage.

1210 Improper water, gas and nutrient exchange can occur due to poor chorioallantoic blood flow  
1211 (Wootton et al., 1977). Thus, viviparous taxa require greater degrees of vascularization and  
1212 vasodilation to facilitate enhanced requirements for maternal resources compared to oviparous  
1213 taxa. Rather than increasing the size of the placenta, increasingly dense blood vessels can support  
1214 fetal growth without compromising space for embryonic growth as occurs in some pigs (Ford,  
1215 1997; Vonnahme et al., 2002). Embryonic vascularization and vasodilation are dependent on  
1216 signals from the endoderm (Jin et al., 2005; Vokes & Krieg, 2002; Wilt, 1965). In oviparous  
1217 individuals of *Saiphos equalis*, populations with extended egg retention, there is expansion of the  
1218 uterine vascular bed and thickening of the chorioallantoic tissue that supports increased

1219 embryonic growth in the later portion of oviparous gravidity (Parker et al., 2010). In the  
1220 viviparous scincid lizard, *Eulamprus quoyii*, angiogenesis, the formation of new blood vessels,  
1221 and expansion of the vessel-dense elliptical area of the uterus is associated with supporting  
1222 increased embryonic oxygen demand (Murphy et al., 2010).

1223       Several protein-coding genes are known to be involved with angiogenesis, vascularization,  
1224 and vasodilation in utero. One study that examined expression patterns across chickens  
1225 (oviparous), horses (viviparous), two viviparous squamates, and one oviparous squamate found  
1226 that no examined genes for angiogenesis showed a viviparity-specific expression pattern  
1227 (Griffith, Brandley et al., 2017). However, other than the chicken, the only oviparous taxa  
1228 included in this study was a reproductively bimodal skink, *Lerista bougainvillii* (Griffith,  
1229 Brandley et al., 2017). Alternatively, differential gene expression analyses on oviparous and  
1230 viviparous individuals of *Zootoca vivipara*, revealed pathways for angiogenesis enriched in  
1231 viviparous female reproductive tissues; and pathways for angiogenesis were enriched across  
1232 genes under divergent selection in oviparous and viviparous *Z. vivipara* individuals.

1233       In the uterine tissue of gestating viviparous skinks and rats, several genes for angiogenesis  
1234 are upregulated—*EPASI*, *HIF1A* and *VEGFA* (Brandley et al., 2012; Whittington et al., 2015,  
1235 2017). Other proteins involved in vascularization and vasodilation in utero include members of  
1236 the vascular endothelial growth factor (*VEGF*) gene family, VEGF receptors (*VEGFRs*),  
1237 placental growth factor (*PGF*) and nitric oxide synthase (*NOS*) (Blomberg et al., 2010; Chen,  
1238 Wang et al., 2015; Gilbert, 2010; Reynolds et al., 2006; Risau, 1997; Torry et al., 2003;  
1239 Vonnahme et al., 2001). In *Saiphos equalis*, different homologs of *NOS* experience different  
1240 patterns of gene expression across the oviparous and viviparous stages of gestation/gravidity  
1241 (Foster et al., 2020). One homolog of *NOS* is upregulated during oviparous late gestation, and

1242 another is upregulated during viviparous late gestation (Foster et al., 2020). Several genes  
1243 involved with angiogenesis and vascular morphogenesis are downregulated in the pre-  
1244 implantation uterus of a marsupial, the Fat Tailed Dunnart, *Sminthopsis crassicaudata*—  
1245 *ADGRA2*, *ADGRB2*, *ANGPTL1*, *EPHB4*, *ISM1*, *PDZRN3*, *RHOJ*, *TNMD*, and *VEGFD*  
1246 (Whittington et al., 2018).

1247 In humans, immune factors are also responsible for increasing embryonic blood supply.  
1248 Embryonic non-classical MHC class I molecule, HLA-G, and uterine natural killer (uNK) cells  
1249 support increased embryonic blood supply (Moffett & Loke, 2006; Rajagopalan et al., 2006). A  
1250 similar pattern of utilizing immune properties to support embryonic blood supply has not been  
1251 yet identified in squamates.

1252 Lipids are a main energy source for embryos. Lipoprotein lipase (LPL) is an important  
1253 enzyme in lipid transport. LPL is significantly expressed on the syncytiotrophoblasts, specialized  
1254 placental cells, of humans (Lindegaard et al., 2005) and the endometrium of cows (Forde et al.,  
1255 2011), and pigs (Ramsay et al., 1991), where it plays a role in lipid mobilization. A viviparous  
1256 lizard, *Pseudemoia entrecasteauxii*, increases capacity for lipid transport toward the end of  
1257 pregnancy (Griffith, van Dyke & Thompson, 2013). The uterine tissue of the yolk-sac placenta in  
1258 this species had significantly higher expression of LPL than the uterine tissues of the  
1259 chorioallantoic placenta (Griffith, van Dyke & Thompson, 2013), leading the authors to suggest  
1260 that the yolk-sac placenta is the major site of lipid transport. LPL expression was not detected  
1261 during pregnancy in the viviparous skink, *Chalcides ocellatus* (Blackburn, 1992; Brandley et al.,  
1262 2012). Instead, lipid transport may be facilitated by fatty acid binding proteins in this species  
1263 (Chmurzyńska, 2006; Brandley et al., 2012). These are also active on mammalian placenta  
1264 (Haggarty, 2002).

1265 Apolipoproteins are also suitable candidates for transport of fatty acids, cholesterol, and  
1266 phospholipids. Five of these (*APOA1*, *APOA2*, *APOA4*, *APOE*, and *APOM*) and *APOA1BP* are  
1267 significantly upregulated in the pregnant uterus of the viviparous skink, *Chalcides ocellatus*  
1268 (Brandley et al., 2012). *APOA1BP* is also upregulated in the uterus of the chorioallantoic  
1269 placenta and yolk-sac placenta compared to non-gestational uterine tissues in *Pseudemoia*  
1270 *entrecaeauxii* (Griffith et al., 2016). Additionally, upregulation of 136 genes that encode solute  
1271 carrier proteins (SLCs) in the pregnant uterus of *Chalcides ocellatus* are associated with  
1272 transport of inorganic ions, metals, glucose, amino acids, peptides, fatty acids, and carboxylic  
1273 acids (Brandley et al., 2012).

1274 Supply of amino acids is required for embryonic development. SLCs have important  
1275 transport functions, including the transport of amino acids, and thus they are considered to be  
1276 important for gestation (Foster et al., 2022). However, a recent study found no overlap in the  
1277 amino acid transporting SLCs upregulated in placentas of viviparous placentrophic vertebrates  
1278 studied, which included eight representatives from Mammalia, Reptilia, and Chondrichthyes  
1279 (Foster et al., 2022). However, *SLC38A3* was upregulated in all viviparous species except *Rattus*  
1280 *norvegicus* (Foster et al., 2022).

1281 Cathepsins and phospholipases are important for uterine secretions for embryonic  
1282 development in horses, pigs, sheep, and cattle (Bazer, 1975; Satterfield et al., 2007; Song et al.,  
1283 2010). Cathepsins are present in yolk sacs of humans and mice. They function to degrade  
1284 proteins to free amino acids (Cindrova-Davies et al., 2017). Two genes for cathepsin L (*CTSL1*  
1285 and *CTSL2*) are upregulated in the uterus during gestation in *Chalcides ocellatus* (Brandley et al.,  
1286 2012). *CTSL* is also upregulated in the uterus during the pre-implantation phase in the Fat-Tailed  
1287 Dunnart, *Sminthopsis crassicaudata* (Whittington et al., 2018), and in the uterus of the

1288 chorioallantoic placenta and uterus of the yolk sac placenta during gestation in *Pseudemoia*  
1289 *entrecasteauxii* (Griffith et al., 2016).

1290 In viviparous individuals of the reproductively bimodal lizard, *Saiphos equalis*, many genes  
1291 for cellular adhesion are upregulated during late gestation (Foster et al., 2020). The authors  
1292 postulated that this helps facilitate maternal-fetal signaling and paracellular transport (Foster et  
1293 al., 2020). Gao et al. (2019) identified a set of genes in *Phrynocephalus vlangalii* that were  
1294 differentially expressed in the uterus during the stage of placentation and these enriched GO  
1295 terms functionally related to the process of placentation. This included an estrogen receptor  
1296 (*ESRI*) and two growth factor receptors (*GHR* and *IGFIR*) (Gao et al., 2019).

1297 Finally, the proteomes of the ovary and placenta from obligately placentrophic *Mabuya*  
1298 lizards can further serve as a useful resource for examining nutrient provisioning in squamates  
1299 (Hernández-Díaz et al., 2017). In the placenta they found protein expression involved with  
1300 nutrient metabolism, transport, protein synthesis, and embryonic development (Hernández-Díaz  
1301 et al., 2017).

1302

### 1303 (5) Uterine glands: adenogenesis, placenta development and histotrophy

1304 In addition to their role in eggshell deposition in oviparous taxa, uterine glands also secrete  
1305 growth factors and cytokines that support placental development in mammals. In humans, these  
1306 include transforming growth factor- $\beta$  (TGF- $\beta$ ), epidermal growth factor (EGF), vascular  
1307 endothelial growth factor (VECG), and leukemia inhibitory factor (LIF) (Hempstock et al.,  
1308 2004). In eutherians, TGF- $\beta$  supports placental development by regulating proliferation and  
1309 invasion rates of placental cells lines (Caniggia et al., 2000; Hempstock et al., 2004; Lafontaine  
1310 et al., 2011).

1311 Histotrophy (also called histiotrophy) occurs when nutrients are secreted into the uterine  
1312 lumen from vesicles of the columnar epithelial cells of the uterus and taken up by the embryo.  
1313 Histotrophic nutrient provisioning is documented across amniotes including marsupials  
1314 (Whittington et al., 2018), several ungulate taxa (Bazer et al., 2011; Han et al., 2016; Gao et al.,  
1315 2009), humans (Burton et al., 2002), and appear to occur in some viviparous squamates (van  
1316 Dyke et al., 2014). In humans, histotrophic nutrient provisioning occurs during the first trimester.  
1317 The intervillous space is filled with fluid containing uterine gland secretions that get  
1318 phagocytosed by the syncytiotrophoblasts and are the initial nutrient source for the fetus (Burton  
1319 et al., 2002). Two of these glycoproteins are epithelial mucin (*MUC1*) and glycodefin A (*GdA*)  
1320 (Burton et al., 2002). Interestingly, the *MUC15* gene is upregulated during gravidity/gestation in  
1321 the uterus of oviparous and viviparous *Saiphos equalis* individuals (Foster et al., 2020). This also  
1322 occurs in the chorioallantoic placenta of *Pseudemoia entrecasteauxii* during gestation (Griffith et  
1323 al., 2016). Several mucins are expressed in the uterus in non-gravid and gravid samples from  
1324 oviparous individuals of *Lerista bougainvillii* and *Lampropholis guichenoti* (Griffith et al.,  
1325 2016).

1326 A survey of viviparous squamates with modest to extensive placentrophy revealed  
1327 prevalence of histotrophic nutrient provisioning rather than hemotrophy, transfer of nutrients  
1328 between maternal and fetal blood streams (Blackburn 2015). Embryos of *Chalcides chalcides*  
1329 have extensive placentrophy that supports substantial maternal nutrient provisioning and  
1330 histotrophy (Blackburn, 2015a). Histotrophy may lessen parent-offspring conflict and give the  
1331 mother the control over nutrient provisioning compared to hemotrophy (Blackburn, 2015b).

1332 *Chalcides ocellatus* has less extensive placentrophy than *C. chalcides* but the gestating uterus  
1333 still illustrates expression of many genes associated with organic and inorganic nutrient transport

1334 (Blackburn, 2015a). Multiple *TGF-β* genes are differentially expressed in the uterus during  
1335 gestation in *C. ocellatus*, however most these are downregulated compared to non-gestational  
1336 uterine tissue (Murphy et al., 2012). The influence of *TGF-β* on placental development and  
1337 nutrient provisioning in *Chalcides spp.* remains to be explored to my knowledge. A TGF-β  
1338 receptor (*TGFBRI*) was associated with placental development in *Phrynocephalus vlangalii*  
1339 (Gao et al., 2019).

1340 Essential to histotrophy is adenogenesis, the generation of endometrial glands. Adenogenesis  
1341 allows for the secretion of histotrophs. The period of early development during which  
1342 adenogenesis occurs is highly variable among vertebrates but it is required for embryonic  
1343 survival (Gray et al., 2001, 2002; Spencer & Bazer, 2004). Some genes involved with  
1344 adenogenesis in sheep are insulin-like growth factor 1 (*IGF-1*), *IGF-2*, *PAX2*, *LHX1* (also known  
1345 as *LIM1*) and *EMX2*, genes in the abdominal-B HOXA cluster, members of both *Wnt* and  
1346 Hedgehog (*Hh*) gene families (Fazleabas et al., 2004), prolactin (*PRL*), fibroblast growth factor 7  
1347 (*FGF7*), *FGF10*, *FGFR2IIIb*, hepatocyte growth factor (*HGF*), a receptor tyrosine kinase (*c-*  
1348 *Met*), and cadherins (Fazleabas, 2007).

1349 In the gestating uterus of *Chalcides ocellatus*, insulin-like growth factor-binding protein 5  
1350 (*IGFBP5*) is one of the most significantly downregulated genes compared to non-gestational  
1351 uterine tissue (Brandley et al., 2012). *IGFBP5* is evolutionarily conserved and multifunctional,  
1352 with an important role in regulating IGF signaling, including that of *IGF-1* and *IGF-2* (Duan &  
1353 Allard, 2020). Other than adenogenesis in sheep, IGFs serve an important role in the growth of  
1354 fetal and maternal tissues in mammals (Gibson et al., 2001; Kampmann et al., 2019).

1355 Genes involved with histotrophic secretion in the marsupial *Sminthopsis crassicaudata*  
1356 include *AP4SI*, *HYOU1*, and *SRPRA* (Whittington et al., 2018). Nutrient transporters

1357 significantly upregulated at this time are *APOL6* (cholesterol transport (Baardman et al., 2013)),  
1358 *PLA2G10* (hydrolysis of fatty acids during pregnancy (Miele et al., 1987)) and a wealth of SLCs  
1359 (solute carrier proteins for transport of sugar, ions, anions, glucose, fatty acids, calcium and zinc  
1360 (Whittington et al., 2018)). Subsequent research has identified downregulated of *HYOUI* at early  
1361 and mid-gestation; and downregulation of *SRPRA* at mid-gestation in viviparous *Zootoca*  
1362 *vivipara* compared to oviparous (Recknagel et al., 2021a). In a reproductively bimodal skink,  
1363 *Saiphos equalis*, *PLA2G10* is upregulated during viviparous late gestation compared to oviparous  
1364 late gestation (Foster et al., 2020). Upregulation of SLCs also occurs in the viviparous skink  
1365 *Chalcides ocellatus* (Brandley et al., 2012; Van Dyke et al., 2014) and in the uterus during  
1366 pregnancy in the grey short-tailed opossum, *Monodelphis domestica* (Hansen, Schilkey & Miller,  
1367 2016).

1368 Uterine glands are also important for secretions of eggshell precursors. I speculate that genes  
1369 involved with adenogenesis of uterine glands may be similarly used to support histotrophic  
1370 nutrient provisioning during transitions to viviparity, but further research is necessary.

1371 Specialized uterine areolar glands are found in some *Mabuya* lizards, a genus with oviparous  
1372 species and viviparous species that utilize placentrophy and histotrophy (Corso et al., 1988,  
1373 2000; Jerez & Ramírez-Pinilla, 2001; Ramírez-Pinilla, 2006; Vieira et al., 2007; Visser, 1975).

1374 Transcriptomic research focused on histotrophic nutrient provisioning, placental development,  
1375 and secretions of eggshell precursors in oviparous and viviparous *Mabuya spp.* would  
1376 complement literature on the genus.

1377

1378 (6) *Discussion & future directions—embryonic nutrients, gas, and water supply*



1379 Many genes for placental functions in mammals have deep origins in vertebrates (Rawn &  
1380 Cross, 2008). In pairwise comparisons of different viviparous amniotes, there is overlap in  
1381 hormones and proteins (SLC superfamily, insulin-like growth factors, aquaporins and solute  
1382 carrier proteins, etc.) involved in uterine remodeling, placentation, and placental transport. While  
1383 shared genes are recruited to the uterus across viviparous amniotes (Recknagel et al 2021a), there  
1384 are no shared genes recruited to the placenta across viviparous reptiles, mammals, and sharks  
1385 (Foster et al., 2022). Evolutionarily, this suggests higher conservation of the regulatory networks  
1386 associated with uterine responses to viviparity than placental responses to viviparity. The  
1387 relationship of these findings to embryonic nutrient provisioning and the evolution of the  
1388 amniotic egg requires further investigation. Supplementary Table 2 illustrates how genes  
1389 mentioned in text for water, gas, and nutrient transport are expressed in reproductive tissues of  
1390 squamates during gestation and gravidity.

1391 If specific genes or physiological processes impact more than one of the Main Five  
1392 categories, it could have a disproportionate influence on transitions. Such an overlap has already  
1393 been identified in *Zootoca vivipara*, where 11 genes are associated with both eggshell traits and  
1394 gestation length (Recknagel et al., 2021a). The solute carrier (*SLC*) gene superfamily is involved  
1395 with both nutrient transport (Brandley et al., 2012; Whittington et al., 2018) and eggshell  
1396 deposition (Yang et al., 2020). Adenogenesis is essential for histotrophic nutrient provisioning  
1397 and secretion of eggshell precursors. Additionally, progesterone production influences both  
1398 uterine quiescence, which is an important state to maintain in lengthened embryonic retention,  
1399 and it also inhibits hepatic vitellogenesis, an important process for lecithotrophic nutrient  
1400 provisioning. Thus, examining the role of *SLC* gene superfamily members, processes of

1401 adenogenesis, and progesterone production during embryonic development in oviparous and  
1402 viviparous squamate may reveal how interconnectivity of the Main Five are.

1403

## 1404 **V. Embryonic Calcium Provisioning**

1405

1406 The embryonic growth stage requires the greatest demand of calcium (Ecay et al., 2017;  
1407 Packard & Packard, 1984; Stewart & Ecay, 2010). To support this, peak uterine concentrations  
1408 of calcium are highest during either eggshell deposition or during the embryonic growth stage, in  
1409 oviparous and viviparous taxa, respectively (Linville et al., 2010; Stewart et al., 2009).  
1410 Regardless of parity mode, embryonic metabolism drives calcium uptake (Packard & Packard,  
1411 1984). The calcium source(s) utilized have clade-specific implications on the genomic and/or  
1412 physiological changes required to transition between parity modes.

1413

### 1414 *(1) Phylogenetic context of embryonic calcium sources*

1415 Calcium can be acquired by the embryo in three forms: calcium carbonate in the eggshell,  
1416 calcium bound to proteins and lipids in the yolk, and/or free ionic calcium from maternal  
1417 delivery through the placenta (Stewart & Ecay, 2010). These correspond with five calcium  
1418 mobilization patterns: 1) Birds, turtles and crocodiles predominately depend on the eggshell; 2)  
1419 Most squamates, regardless of parity mode, predominately depend on the yolk; 3) Some  
1420 squamate species are reliant on both the eggshell and yolk; 4) Some viviparous squamate species  
1421 are reliant on both the yolk and placenta; and 5) therian mammals and rare viviparous squamates  
1422 predominately depend on the placenta (Blackburn, 2015a; Hoenderop, Nilius, & Bindels, 2005;  
1423 Jenkins & Simkiss, 1968; Kovacs, 2015; Packard, 1994; Packard & Seymour, 1997; Stewart et

1424 al., 2009, 2009; Stewart & Ecy, 2010; Thompson, Stewart et al., 1999; Thompson, Stewart, &  
1425 Speake, 2000; Ramírez-Pinilla, 2006).

1426 From an evolutionary perspective, squamate eggs might serve as the best models of the  
1427 ancestral amniote egg. Unlike birds, oviparous squamates generally rely on yolk calcium rather  
1428 than eggshell calcium. The yolk sac of non-avian reptiles is a good model for the transition  
1429 between the egg of anamniotes and amniotes (Blackburn, 2020). Taken together and given that  
1430 hard calcified eggshells of Archelosaurs are likely derived (as discussed in section III.3)—  
1431 squamate eggs may have the closest resemblance to the ancestral amniote egg. Interestingly, to  
1432 my knowledge, oviparous squamates do not sequester calcium from the eggshell into the yolk  
1433 during incubation (Packard, 1994).

1434

1435 *(2) Hypotheses on calcium mobilization and the evolution of parity modes*

1436 It was hypothesized that predominant reliance on eggshell calcium should constrain lineages  
1437 to oviparity because the evolution of viviparity would result in a lost calcium source (hereafter  
1438 eggshell calcium constraint hypothesis) (Stewart & Ecy, 2010; Packard et al., 1977; Packard &  
1439 Packard, 1984). This hypothesis suggested that viviparity should only evolve in lineages  
1440 predominately reliant on yolk calcium (Packard et al., 1977; Packard & Packard, 1984).

1441 Fittingly, birds, turtles and crocodilians generally rely on eggshell calcium, and they are  
1442 constrained to oviparity (Anderson et al., 1987). The eggshell calcium constraint hypothesis  
1443 holds true for most viviparous squamates that rely heavily on yolk calcium (Stewart & Castillo,  
1444 1984; Stewart & Ecy, 2010; van Dyke et al., 2014).

1445 Subsequent research revealed that viviparity is not constrained by a prerequisite reliance on  
1446 yolk calcium. Oviparous scincid skinks studied thus far are intermediately reliant on eggshell and

1447 yolk calcium (Linville et al., 2010; Shadrix et al., 1994; Stewart et al., 2009; Stewart &  
1448 Thompson, 1993; Thompson et al., 2001). Calcium placentrophy contributes substantially to  
1449 embryonic development in several viviparous squamates including *Pseudemoia entrecasteauxii*,  
1450 *Eulamprus quoyi*, *Zootoca vivipara*, *Saiphos equalis*, and a species of *Mabuya* lizard (Ecay et al.,  
1451 2017; Linville et al., 2010; Ramírez-Pinilla, 2006; Ramírez-Pinilla et al., 2011; Stewart &  
1452 Thompson, 1993). These taxa, with the exception of *Zootoca vivipara*, are in the family  
1453 Scincidae (Burbrink et al., 2020), which is also the family with the most independent origins of  
1454 viviparity in squamates (Blackburn, 1982, 1999; Pyron & Burbrink, 2014).

1455 To understand the breadth of physiological conditions from which oviparity and viviparity  
1456 evolve in squamates, future research should examine calcium transport in other lineages. Studies  
1457 focused on snakes would be particularly informative given the sparse literature on them.

1458 *Helicops angulatus*, a reproductively bimodal water snake from South America, is an ideal  
1459 model for this (Braz et al., 2016). Thus far, many oviparous snakes are known to be  
1460 intermediately reliant on yolk and eggshell calcium. This has not precluded viviparity from  
1461 evolving in these lineages.

1462 The presence of embryos during extended embryonic retention may trigger positive feedback  
1463 stimuli for continued uterine calcium secretions which may support placental calcium transport,  
1464 and thus incipient calcium matrotrophy (Stewart & Ecay, 2010). This is postulated to resemble  
1465 the hormonal and mechanical stress mechanisms implicated in avian eggshell formation and  
1466 uterine calcium secretions (Bar, 2009a; Stewart & Ecay, 2010). The influx of calcium late in  
1467 viviparous gestation may be triggered in part by embryonic growth that over distends the uterus.  
1468 This is seen in studies on myometrial stretch in mammals when uterine overdistention triggers  
1469 spikes in calcium (Kao & McCullough, 1975; and see e.g. Wray et al., 2015).

1470       Dramatic changes to activity in chorioallantois should not be required during parity mode  
1471 transitions because these homologous tissues (Metcalf & Stock, 1993) transport calcium  
1472 regardless of parity mode (Ecay, Stewart & Blackburn, 2004; Tuan & Scott, 1977; Tuan &  
1473 Knowles, 1984; Tuan et al., 1978, 1986). Specialized placental structures in some viviparous  
1474 squamates enhance calcium provisioning but specialization is not required for placental calcium  
1475 transport (Stewart et al., 2009; Stewart & Ecay, 2010; Thompson et al., 2000). Loss of  
1476 chorioallantoic calcium transporting capacity would be disadvantageous to either parity mode.  
1477 Growing research reveals that, like mammals, placentrophy and viviparity can evolve  
1478 concurrently in squamates (Blackburn, 2015a; Ecay et al., 2017; Stewart & Ecay, 2010).

1479       Placing these previously proposed models in a phylogenetic context, the calcium transport  
1480 method of oviparous ancestors likely has an influence on the method of calcium transport used  
1481 for viviparous taxa—matrotrophic calcium provisioning, lecithotrophic calcium provisioning, or  
1482 a combination of the two. Consistent with the basal cap hypothesis—when viviparity arises from  
1483 oviparous ancestors with embryos that depended predominately on eggshell calcium, this should  
1484 favor a transition to viviparity via incipient calcium matrotrophy because the chorioallantois  
1485 already plays the major role in transporting calcium from the eggshell to the embryo. Since the  
1486 reproductive mode and calcium provisioning of oviparous ancestors are essentially unknown,  
1487 researchers can use the closest oviparous relatives as proxies. Similarly, viviparous taxa that are  
1488 in close phylogenetic proximity to oviparous taxa that depend on lecithotrophic calcium  
1489 provisioning should remain reliant on yolk calcium. Together, these guidelines provide a  
1490 framework from which researchers can form hypotheses about the calcium provisioning method  
1491 of a viviparous lineage if the calcium provisioning method of oviparous close relatives are  
1492 known, or vice versa. Measurements of the proportional contribution of different calcium sources

1493 during development has only been done in select taxa (e.g. Packard, 1994; Stewart, 2013;  
1494 Stewart & Ecy, 2010; Stewart, Ecy & Blackburn 2004). Once validated, the framework (i.e.,  
1495 the calcium provisioning method of close relatives) can help increase the speed at which science  
1496 measures and infers the evolutionary history of calcium provisioning across amniotes and  
1497 squamates. Collection of this data across the squamate phylogeny may enable assignment of  
1498 these hypotheses to specific clades.

1499 Embryonic calcium source could have implications on the physiological changes required to  
1500 transition between parity modes. Reliance on yolk calcium should render, essentially, no  
1501 mechanistic changes for calcium transport. On the other hand, incipient calcium matrotrophy  
1502 requires regulatory changes in the uterus, like timing of calcium secretions (Griffith et al., 2015).  
1503 However, regardless of parity mode 1) the uterus secretes calcium, 2) the chorioallantois  
1504 transports calcium and 3) embryonic metabolism drives uptake of calcium. Assuming maternal  
1505 tissue remains responsive to embryonic metabolism, the joint evolution of matrotrophic calcium  
1506 provisioning with viviparity may require little to no physiological adjustments.

1507 The diversity of embryonic calcium provisioning patterns in viviparous squamates may not  
1508 be fully explained by the eggshell calcium constraint hypothesis (Packard et al., 1977; Packard &  
1509 Packard, 1984) or incipient calcium matrotrophy (Stewart & Ecy, 2010). Both hypotheses  
1510 implicitly assume that viviparity equates to a lost eggshell. In one viviparous squamate, *Haldea*  
1511 *striatula*, and in viviparous populations of two reproductively bimodal lizards, *Zootoca vivipara*  
1512 and *Saiphos equalis*, the calcified eggshell is considered as a component of the placenta (Stewart,  
1513 2013). Some other viviparous squamates have transient calcified patches on their embryonic  
1514 membranes (Blackburn, 1998; Heulin, 1990, 2005; Qualls, 1996) suggesting that uterine calcium  
1515 secreting capabilities in early gestation may be retained in some viviparous lineages. In the case

1516 of reversals, it remains unknown how the uterus shifts back to early calcium secretions after  
1517 ovulation (Blackburn, 2015b; Griffith et al., 2015).

1518

1519 *(3) Embryonic calcium provisioning mechanisms*

1520 In vertebrates, specialized tissues that recover environmental calcium and transport it into  
1521 blood circulation maintain conserved mechanisms for intracellular calcium transport (Bronner  
1522 2003; Hoenderop et al., 2005). These include the uterus, chorioallantoic tissues, and yolk  
1523 splanchnopleure (Bronner, 2003; Hoenderop et al., 2005; Stewart, 2013). Therefore, uterine and  
1524 embryonic tissues may be pre-adapted for maternal and embryonic calcium provisioning.

1525 In birds, a sub-compartment of the mammillary layer of the eggshell is the calcium reserve  
1526 body (Chien et al., 2009), which contains microcrystals of calcite that get dissolved and  
1527 transported as calcium to the embryo (Chien et al., 2009). Calcium is eroded from the eggshell  
1528 by acid released from villus cavity cells (VCCs) in chorioallantoic membrane (Anderson, Gay,  
1529 and Schraer, 1981; Narbaitz et al., 1981; Packard & Lohmiller, 2002; Simkiss, 1980). This  
1530 increases the carbonic anhydrase activity of the cells enabling calcium to be released into the  
1531 cavity between the eggshell and the chorionic epithelium, where it is taken up by capillary  
1532 covering cells (CCCs) in chorioallantoic membrane (Coleman & Terepka, 1972). In some  
1533 species this erosion leads to a gradual weakening of the eggshell that facilitates hatching (Chien,  
1534 Hincke & McKee, 2008). In chickens, transcalcine, a calcium binding protein, is credited for the  
1535 calcium transporting capacity of the chorioallantoic membrane (Tuan & Knowles, 1984; Tuan &  
1536 Ono, 1986; Tuan & Scott, 1977; Tuan et al., 1978, 1986). The presence of VCCs and CCCs in  
1537 the chorioallantois of viviparous squamates would indicate a known route through which calcium  
1538 can be absorbed.

1539 Transcellular calcium transport has been modeled as a three-step process involving proteins  
1540 calbindin-D9K, calbindin-D28K, and the highly calcium-specific ion channels of the transient  
1541 receptor potential vanilloid gene family (*TRPV5* and *TRPV6*) (Stewart & Ecaj, 2010). Across  
1542 vertebrates, this machinery is shared in epithelial tissues with significant roles in calcium  
1543 transport (Hoenderop et al., 2005). Estrogen and vitamin D3 have regulatory roles in this  
1544 process.

1545 Calbindin-D9K, calbindin-D28K, *TRPV5*, and *TRPV6* is involved with calcium exchange in  
1546 multiple organs of birds, squamates, and mammals. Broadly, activity of calbindin-D9K and/or  
1547 calbindin-D28K is associated with patterns of calcium absorption in the mammalian kidney and  
1548 uterus (Bindels, 1993; Luu et al., 2004), murine uterus and placenta (Lafond & Simoneau, 2006;  
1549 Koo et al., 2012), and chicken duodenum and uterus (Bar, 2009b; Yang et al., 2013). In humans,  
1550 calbindin-D9K and calbindin-D28K are critical to the active transport of Ca<sup>2+</sup> across placental  
1551 cells (Faulk & McIntyre, 1983; Belkacemi, Simoneau & Lafond, 2002; Belkacemi et al., 2004).  
1552 A study on rats suggests that calbindin-D9K increases by over 100-fold in the last 7 days of  
1553 gestation (Glazier et al., 1992), when the embryo gains the majority of calcium. *TRPV6* is  
1554 involved with maternal-fetal calcium transport in mice (Suzuki et al., 2008). Increased *TRPV6*  
1555 and calbindin-D28K expression occurs during eggshell formation in chickens (Yang et al.,  
1556 2013). Given the involvement of these genes in both eggshell deposition and embryonic calcium  
1557 transport, squamates may have exploited this pathway to support transitions. Expression of these  
1558 genes during gestation or gravidity in squamates has been detected (e.g. calbindin-d9K in  
1559 *Saiphos equalis*, and calbindin-d28k in *Zootoca vivipara*) (Foster et al., 2020; Recknagel et al.,  
1560 2021a), and is expanded upon in the following paragraphs.



1561 In several highly matrotrophic lizards, embryonic uptake of calcium is associated with  
1562 placental expression of calbindin-D28K (Stewart et al., 2009; Stinnett et al., 2011, 2012). In both  
1563 oviparous and viviparous embryos of *Zootoca vivipara*, sharp increase in calcium uptake in late  
1564 development coincides with increased calbindin-D28K and PMCA by the chorioallantois  
1565 (Stewart et al., 2009, 2011). In oviparous corn snakes, *Pantherophis guttatus*, expression of  
1566 calbindin-D28K in the yolk-sac and chorioallantoic membrane coincides with growth of these  
1567 tissues and calcium transport activity (Ecay et al., 2004). The chorioallantois of other lizards and  
1568 snakes transport calcium to the embryo and express calbindin-D28K and PMCA (Blackburn,  
1569 2004; Ecay et al., 2004; Stewart et al., 2010; Stinnett et al., 2012).

1570 Viviparous embryos of *Zootoca vivipara*, a reproductively bimodal lizard, incubated *ex utero*  
1571 respond to availability of calcium by increasing expression of calbindin-D28K (Ecay et al.,  
1572 2017). In this species, embryonic recognition of environmental calcium stimulates a transcellular  
1573 calcium transporting mechanism and may also alter chorioallantoic membrane paracellular  
1574 permeability to calcium (Ecay et al., 2017). The authors proposed that there is a calcium sensing  
1575 receptor (CaSR) on chorionic epithelial cells to support this in both oviparous and viviparous  
1576 *Zootoca vivipara* embryos (Ecay et al., 2017), similar to the CaSRs expressed by vertebrate cells  
1577 involved in calcium homeostasis (Brennan et al., 2013).

1578 As mentioned earlier, PMCA activity is associated with eggshell deposition in birds and  
1579 oviparous squamates (Bar, Rosenberg, & Hurwitz, 1984; Hincke et al., 2012; Wasserman et al.,  
1580 1991). PMCA is also crucial for calcium transport in late embryonic development in rats (Glazier  
1581 et al., 1992). In viviparous scincid lizards, *Niveoscincus metallicus*, *N. ocellatus*, and  
1582 *Pseudemoia spenceri*, PMCA was expressed in uterine glandular and surface epithelia during  
1583 pregnancy but only *P. spenceri* expressed it throughout gestation (Herbert et al., 2006). When

1584 PMCA was not detected by immunoblotting in the yolk splanchnopleure of *Haldea striatula*, a  
1585 viviparous snake that relies predominately on yolk calcium (Stewart, 1989; Fregoso, Stewart, &  
1586 Ecay, 2010), NCXs were proposed as an alternative transporter of calcium (Fregoso et al., 2012).  
1587 NCXs are important for placental calcium transport in humans (Belkacemi et al., 2005).

1588        Calcitropic hormones, those involved with calcium transport, and phosphotropic hormones,  
1589 those involved with phosphorous transport, operate via an interconnected pathway (Andrukhova  
1590 et al., 2016; Biber, Hernando & Forster, 2013; Blaine, Chonchol & Levi, 2015; Erben &  
1591 Andrukhova, 2015). Phospho- and calcitropic hormones are important regulators of fetal serum  
1592 mineral concentrations (Kovacs, 2015). Evidence from viviparous amniotes suggests that these  
1593 are suitable candidates for embryonic calcium provisioning. In mice, genes encoding parathyroid  
1594 hormone (*PTH*) and *PTH*-related peptide (*PTHrP*) are important regulators of placental calcium  
1595 transport (Kovacs et al., 1996; Simmonds et al., 2010). A non-exhaustive list of additional  
1596 candidates for embryonic calcium provisioning include fibroblast growth factor 23 (Bar, 2009a;  
1597 Erben & Andrukhova, 2015; Stewart & Ecay, 2010), the annexin gene family (Matschke et al.,  
1598 2006), carbonic anhydrase (Narbaitz et al., 1981; Tuan & Knowles, 1984), and calcium binding  
1599 proteins (CaBPs) can be found in the referenced literature.

1600

1601        (4) *Discussion & future directions—calcium provisioning and parity mode evolution*

1602        Phylogenetic frameworks enable researchers to make broader testable hypotheses about the  
1603 evolutionary history of calcium provisioning in specific clades. Such a framework is proposed in  
1604 section V.2 to infer ancestral parity modes in the context of calcium provisioning in amniotes.  
1605 Implications gleaned from taxon-specific studies can be explored in distantly related analogous  
1606 groups.

1607 Genes involved with calcium transport in uterine and embryonic tissues have been described  
1608 across mammals, birds, and reptiles. Like other amniotes, activity of calbindin-D28K and PMCA  
1609 supports embryonic calcium provisioning across diverse oviparous and viviparous squamates.  
1610 Their involvement with both eggshell deposition and embryonic calcium provisioning makes  
1611 these particularly interesting candidates for parity mode evolution. The regulatory influence of  
1612 other molecules in calcium transport, like *PTH*, *PTHrP* and NCXs has not been evaluated  
1613 thoroughly in squamates. Additional reviews on mechanisms of embryonic calcium provisioning  
1614 in squamates can be found in the literature (Stewart, 2013; Stewart & Eday, 2010).

1615 Additionally, I add a speculation. Perhaps lineages with incipient calcium matrotrophy more  
1616 feasibly reverse to oviparity because of the continued role of the uterus in calcium provisioning.  
1617 However, this hypothesis only holds up if maternal provisioning of calcium is not synonymous  
1618 with maternal provisioning of all nutrients.

1619

## 1620 **VI. Maternal-Fetal Immune Dynamics**

1621

1622 Medawar (1953) pointed out the paradigm between the peripheral body's normal attack  
1623 response to allografts (foreign tissue) and uterine tolerance to embryos (Medawar, 1953). This  
1624 was inspired by earlier work by Ray Owen (Owen, 1945). Stricter regulation of the maternal and  
1625 fetal immune systems is expected for viviparous reproduction because of contact between uterine  
1626 and embryonic tissues. Oviparity may pose less of an immunological challenge. Medawar  
1627 suggested barriers, inertness and/or immunosuppression enable pregnancy. This formed the  
1628 foundation of decades of medical research on immune dynamics between maternal, embryonic,  
1629 and paternal immune factors in utero.

1630 In recent years, there was a call for a reappraisal of Medawar's paradigm (Chaouat, 2010,  
1631 2016; Moffett & Loke, 2004, 2006; Mor et al., 2011; Stadtmayer & Wagner, 2020b; Yoshizawa  
1632 2016). Moffett & Loke (2006) caution against conceptualizing embryos as analogs of allografts.  
1633 To my knowledge, this perspective has yet to reach the evolutionary literature on squamate  
1634 parity mode evolution (Foster et al., 2020; Graham et al., 2011; Gao et al., 2019; Murphy &  
1635 Thompson, 2011; van Dyke, Brandley, & Thompson, 2014; Murphy, Thompson, & Belov, 2009;  
1636 Recknagel et al., 2021a). Importantly, challenges to Medawar's paradigm do not preclude  
1637 immunological responses to viviparity. They simply suggest that the immune environment of the  
1638 uterus is uniquely evolved to support exposure to foreign tissue.

1639 The uterine immune system has a distinct evolutionary history from the periphery. It enables  
1640 cooperative dynamics with foreign tissues. It supports fertilization and early embryonic  
1641 development. This should have started evolving, distinct from the periphery, since internal  
1642 fertilization first originated. To contextualize this, I discuss the changing landscape of  
1643 immunological research at the maternal-fetal interface and what it means in the context of  
1644 amniote parity mode evolution. Overall, I hope readers consider how the uterus evolved to  
1645 support internal gestation, and which model systems may be appropriate to investigate this.

1646 Most literature on maternal-fetal immune dynamics limits itself to mammals. Squamates may  
1647 serve as a better comparative model for understanding the evolution of the uterine immune  
1648 system. Active research on the peripheral reptilian immune system (Zimmerman et al., 2010,  
1649 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et al., 2017;  
1650 Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights on this.

1651

1652 *(1) Comparing amniote immune systems*

1653 Cellular components of the innate immune system are conserved across jawed vertebrates  
1654 (Uribe et al., 2011; Zimmerman et al., 2010). The general machinery of the adaptive immune  
1655 system is ancient despite divergences and convergences across all domains of life (Ghosh et al.,  
1656 2011; Morales et al., 2017; Müller et al., 2018; Rimer et al., 2014). Diversification of antigen  
1657 receptor genes likely occurred independently in a lineage-specific fashion (Boehm et al., 2018).  
1658 Compared to mammals, the avian immune system requires less antigen (Larsson et al., 1998).  
1659 Birds also have faster but shorter antibody responses, potentially due to their higher body  
1660 temperatures (Zimmerman, 2010).

1661 Reptiles have the same general components of the mammalian immune system (Zimmerman,  
1662 2020). However, the reptilian immune system may not fit neatly into the two arms of mammalian  
1663 immune systems—innate and adaptive (Zimmerman, 2010; 2020). Expanding upon this is  
1664 beyond the scope of this review, but it is worth considering in future evolutionary research.  
1665 Squamates may serve as a better comparative model for understanding the evolution of the  
1666 uterine immune system. Active research on the peripheral reptilian immune system (Zimmerman  
1667 et al., 2010, 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et  
1668 al., 2017; Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights. I  
1669 refer readers to articles by Zimmerman et al. (2010, 2020) and Ghorai et al. (2018), and the book  
1670 by Williams (2012) for more information on the avian immune system.

1671

1672 *(2) Medawar's paradigm*

1673 Tolerance toward the foreign fetus was postulated to occur through immunological inertness,  
1674 immunosuppression or immunotolerance mechanisms (Medawar, 1953). Theoretically,  
1675 immunotolerance could be established if there are relatively small quantities of alloantigens

1676 present, resulting in regulatory responses rather than activating responses (Pradeu, 2011).  
1677 Contradicting this, the larger the alloantigen difference between the mother and embryo the  
1678 bigger and healthier the placenta is in rats (Chaouat et al., 2010). In humans, divergent HLA  
1679 profiles between mother and embryo do not lead to detrimental immune responses (Tilburgs,  
1680 Scherjon, & Claas, 2010). Instead, cooperative inflammatory responses between maternal and  
1681 fetal tissues support reproduction (Stadtmauer et al., 2020a). In humans, microchimeric cell  
1682 populations, presence of cells from one individual in another genetically distinct individual, are  
1683 now considered a normal expectation of pregnancy (Nelson, 2012).

1684 In his 1991 Nobel Lecture, Medawar acknowledged that maternal and embryonic tissues  
1685 have regular exposure to alloantigens (Medawar, 1991). It has become clear that the maternal  
1686 immune system actively responds to fetal alloantigen rather than responding solely with  
1687 ignorance or anergy (Arck & Hecher, 2013). Neither maternal immunosuppression/privilege nor  
1688 embryonic inertness/immaturity fully explain immune dynamics during gestation in mammals,  
1689 including those with the simple epitheliochorial placentation (Chaouat et al., 2010; Chavan,  
1690 Griffith & Wagner, 2017; Moffett & Loke, 2004, 2006; Stadtmauer & Wagner, 2020a).

1691

1692 *(3) Perspectives on the evolution of the uterine immune system*

1693 Viviparous reproduction existed eons before the origin of mammals and, to my knowledge,  
1694 no evidence suggests there was immune conflict within these taxa (Chaouat, 2016). Placentrophy  
1695 existed as far back as the invertebrate clade Bryozoa (Ostrovsky, 2013; Schwaha et al., 2019),  
1696 suggesting an ancient history for supportive maternal-fetal immune dynamics. Differing from  
1697 Medawar's paradigm, Polly Matzinger, who proposed the 'danger model' for the immune system

1698 (Matzinger, 2007), wrote “Reproduction cannot be a danger. It does not make evolutionary  
1699 sense” (Chaouat, 2016).

1700 In mammals, immunological cells at the maternal-fetal interface may not function through  
1701 self-non-self-discrimination, as they are understood to function in the rest of the body (Chaouat,  
1702 2016; Moffett & Loke 2004, 2006). The ‘maternal-fetal interface’ may be better conceptualized  
1703 as ‘maternal-fetal intra-action’ given the dynamics between maternal and fetal immune systems  
1704 in mammals (Yoshizawa, 2016). It is unclear if these insights apply to other viviparous amniotes.

1705 In mammals, immune factors in the uterus and placenta appear to be specifically evolved to  
1706 support maternal-fetal immune dynamics. Several cell types have unique functions and/or  
1707 phenotypes in utero—uterine NK (uNK) cells, uterine macrophages, uterine T regulatory cells  
1708 (Faas & de Vos, 2017; Mold et al., 2008, 2010; Mold & McCune, 2011). An immunosuppressive  
1709 antigen, HLA-G, is almost exclusively expressed by trophoblasts (Faulk & Temple, 1976;  
1710 Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al., 1997). Taken from an  
1711 evolutionary perspective, this suggests that the uterine immune system in viviparous mammals  
1712 evolved unique responses to allogenic tissues that differ from the periphery. Whether the  
1713 evolution of this system predates mammals remains to be explored, to my knowledge.

1714 It is suggested that viviparous reproduction is immunologically compatible in species with  
1715 less active adaptive immune system, like sharks (Chaouat, 2016). In these clades, innate immune  
1716 cells, like uNK cells, may be sufficient to regulate immune responses during pregnancy (Moffett  
1717 & Loke, 2004; Chaouat, 2016). Given that there is an unclear distinction between the innate and  
1718 adaptive immune system in reptiles (Zimmerman, 2020), determining immunological difficulty  
1719 of evolving viviparity in squamates requires further investigation.

1720 In uterine tissue of oviparous and viviparous skinks maternal antigens are expressed prior to  
1721 and during gestation and gravidity (Murphy et al., 2009), but the viviparous species in the study  
1722 have a unique expression profile of MHC antigens which may ‘hide’ the embryo from the  
1723 maternal immune system (Murphy et al., 2009). Similarly, in a reproductively bimodal skink,  
1724 *Saiphos equalis*, both oviparous and viviparous gestation is associated with expression of MHC  
1725 genes (Foster et al., 2020). Regardless of parity mode, *S. equalis* expresses genes associated with  
1726 immunocompetence, including MHC genes including *H2-EA* (Foster et al., 2020). The similar  
1727 profile between the oviparous and viviparous state is attributed to the use of very long egg  
1728 retention utilized by oviparous *S. equalis* (Foster et al., 2020). This highlights that extended  
1729 embryonic retention is accompanied with immunological responses in utero, which is relevant to  
1730 the EER model on amniote origins.

1731 Some of these genes expressed by *S. equalis* are also expressed in viviparous *Chalcides*  
1732 *ocellatus* during gestation including complement component genes (C3, C9) and MHC genes  
1733 (Brandley et al., 2012; Foster et al., 2020). The majority of immune genes expressed during  
1734 gestation/gravidity in *S. equalis* have immunoglobulin receptor binding functions (Foster et al.,  
1735 2020), an important feature of eutherian pregnancy that prevents rejection of the fetus through  
1736 actions of the maternal innate immune system (Alijotas-Reig, Llurba, Gris, 2014)). In another  
1737 reproductively bimodal skink, *Zootoca vivipara*, immune system response genes are enriched in  
1738 the set of genes under divergent selection in oviparous and viviparous genomes (Recknagel et al.,  
1739 2021a).

1740

1741 (4) *Implications of the reptilian immune system and morphology on parity mode evolution*



1742 Ectothermic reptiles may inherently have a more tolerogenic uterine environment compared  
1743 to mammals due to their slower antibody response. It can take up to six weeks to reach peak  
1744 concentrations (Ingram & Molyneux, 1983; Grey, 1963; Marchalonis et al., 1969; Pye et al.,  
1745 2001; Origgi et al., 2001; Work et al., 2000). A slower metabolism also makes several reptiles  
1746 more tolerogenic to pathogens (Ghorai & Priyam, 2018).

1747 During pregnancy in the viviparous skink, *Chalcides ocellatus*, there is a reduced response to  
1748 in vitro exposure to mitogens concanavalin A (Con A), phytohemagglutinin (PHA), and  
1749 *Escherichia coli* lipopolysaccharide (LPS) (Saad & El Deeb, 1990). Oviparous lizards exhibit  
1750 immune activation tradeoffs during reproductive cycles (Cox, Peadar, & Cox, 2015; Durso &  
1751 French, 2018; French, Johnston, & Moore, 2007; Uller, Isaksson, & Olsson, 2006).

1752 In the majority of viviparous squamates, the eggshell membrane is absorbed during  
1753 pregnancy (Blackburn, 1993). In mammals, epitheliochorial placentation (the most superficial  
1754 and non-invasive placenta type) is sufficient to cause immunorecognition from the mother.  
1755 Specialized placental cells, trophoblasts, may be more common in other viviparous vertebrates  
1756 than previously recognized (Blackburn, 2015a). For example, a gene with fusogenic properties  
1757 characteristics of trophoblast syncytins was recently identified in the *Mabuya* lizard placenta  
1758 (Cornelis et al, 2017). In mammals, trophoblasts are antigen presenting and actively participate  
1759 in maternal-fetal immune dynamics.

1760 A few viviparous squamates have placentas with characteristics similar to placentas found in  
1761 eutherian mammals—syncytialized cells layers, specialized zones such as areolae and  
1762 placentomes, or cellular invasion of maternal tissues by the fetus (Blackburn & Flemming, 2012;  
1763 Jerez & Ramírez-Pinilla, 2001; Vieira et al., 2007). The increased contact here may require more

1764 tightly regulated immune dynamics at the maternal-fetal interface compared to other viviparous  
1765 squamates.

1766

1767 (5) *The inflammation paradox*

1768 In mammals, implantation evolved from an ancestral inflammatory attachment reaction  
1769 (Griffith, Chavan et al., 2017). Inflammation is the most crucial system to support implantation,  
1770 but it is also the greatest threat to the continuation of pregnancy (Chavan et al., 2017). This  
1771 phenomenon is called the inflammation paradox. In humans, immune cells including uterine  
1772 macrophages, T cells of multiple subtypes, uterine natural killer (uNK) cells, dendritic cells, and  
1773 natural killer T (NKT) cells increase until implantation and remain abundant in the uterus  
1774 throughout first trimester (Bulmer et al., 1991; Bulmer, Williams & Lash, 2010). Early  
1775 implantation in humans is characterized by high pro-inflammatory T helper (Th)-1 cells and  
1776 cytokines (IL-6, IL-8, and TNF $\alpha$ ) (Yoshinaga, 2008). The exploitation of inflammatory  
1777 mechanisms for eutherian implantation and the shift toward non-inflammatory activity to  
1778 maintain pregnancy may have been key in enabling extended embryonic retention of eutherians  
1779 (Griffith, Chavan et al., 2017).

1780 How the inflammation paradox applies to viviparous squamates is unclear, given that  
1781 placentation in squamates and mammals is not homologous (Griffith, Van Dyke, & Thompson,  
1782 2013). In extrauterine pregnancies of mammals with non-invasive placentas, the embryo will  
1783 invade extrauterine tissue because it is not inhibited by uterine secretions (Vogel, 2005; Samuel  
1784 & Perry, 1972). However, in *Pseudemoia entrecasteauxii*, a viviparous skink that also has a non-  
1785 invasive placenta, extrauterine pregnancy does not result in invasive implantation of extrauterine  
1786 tissues (Griffith, Van Dyke, & Thompson, 2013). The inherent invasive nature of mammalian

1787 embryos outside of the uterus, compared to the non-invasive nature of viviparous squamate  
1788 embryos studied thus far, suggests that the parent-offspring conflict and the inflammation  
1789 paradox may be less pronounced in viviparous squamates compared to viviparous mammals.

1790

1791 *(6) Inertness and barriers at the maternal-fetal interface*

1792 The uterine environment is not inert or sterile (Agostinis et al., 2019; Erlebacher, 2013;  
1793 Moffett & Loke, 2006; Munoz-Suano, Hamilton, & Betz, 2011; Murphy, Thompson, & Belov,  
1794 2009; Yoshimura, Okamoto, & Tamura, 1997). In humans, the decidual layer of the uterus  
1795 during pregnancy is comprised of ~40% leukocytes (Ander, Diamond, & Coyne, 2019; Manaster  
1796 & Mandelboim, 2010). This cellular subpopulation has 70% uNK cells, 10-20% antigen  
1797 presenting cells (APCs) including macrophages and dendritic cells, and 3-10% T cells of several  
1798 subtypes (Abrahams et al., 2004; Hanna et al., 2006; Kämmerer et al., 2006; Le Bouteiller &  
1799 Piccinni, 2008; Liu et al., 2017; Manaster & Mandelboim, 2010; Moffett-King, 2002; Moffett &  
1800 Loke, 2006; Roussev et al., 2008). There is an abundance of decidual large granular lymphocytes  
1801 (LGLs), CD3-NK cells and CD3+ activated cytotoxic T cells, in the human uterus, that have  
1802 cytotoxic properties and produce cytokines, and these are affected by fetal MHC molecules  
1803 (Rieger, 2002).

1804 Birds also have immunocompetent cells in their oviducts. T and B cells are present in  
1805 chicken ovary where they are stimulated by estrogen (Barua & Yoshimura, 1999; Withanage et  
1806 al., 2003; Zettergren & Cutlan, 1992). Other immunocompetent cells in the chicken oviduct  
1807 include IgG+, IgA+ and CD3+ (Yoshimura, Okamoto, & Tamura, 1997). Immune competent  
1808 cells located throughout the mucosal tissue of avian oviductal segments including macrophages,

1809 antigen presenting cells (APCs) expressing MHC class II antigens, helper T cells and cytotoxic T  
1810 cells, and premature B cells (Das, Isobe, & Yoshimura, 2008).

1811 Inert barriers between maternal and fetal tissues may 'hide' the embryo. In oviparous taxa,  
1812 the eggshell may serve as a barrier. However, the antimicrobial properties of the eggshell matrix  
1813 in birds demonstrate that even the eggshell is not inert. The FAS ligand, also called APO-1 or  
1814 CD95, in humans and rodent embryonic tissue was proposed to serve as a barrier because it  
1815 causes apoptosis of surrounding maternal immune cells (Kayisli et al., 2003; Makrigiannakis et  
1816 al., 2008).

1817 Medawar suggested that an impermeable placenta strictly regulates molecular exchanges,  
1818 preventing rejection of the embryo (Medawar, 1991). Syncytiotrophoblasts lack cellular junctions  
1819 and thus it was postulated to serve as this barrier (Ander et al., 2019). However, the growing data  
1820 on bidirectional cellular traffic of APCs, even in mammals with noninvasive placentas, rejected  
1821 this hypothesis (Bakkour et al., 2014; Burlingham & Bracamonte-Baran, 2015; Fujiki et al.,  
1822 2008; Turin et al., 2007).

1823

#### 1824 *(7) T cell populations and mammalian viviparity*

1825 In mammals, immune-dynamics at the maternal-fetal interface are established through  
1826 innate and adaptive immune responses. There is a delicate balance between ratios of Th1, Th2,  
1827 Th17, Tregs and memory T cells at the maternal-fetal interface in eutherian mammals during  
1828 gestation (Chaouat et al., 1997; Kieffer et al., 2019; Peck & Mellins, 2010; Saito et al., 2010; Wu  
1829 et al., 2014). A shift in utero from T helper type 1 (Th1) cells to T helper type 2 (Th2) cells  
1830 during gestation in mammals equates to a shift from pro-inflammation to anti-inflammation. The  
1831 galectin proteins, GAL-13 and GAL-14, expressed by syncytiotrophoblasts, bind to T cells

1832 where they inhibit activation, induce apoptosis, and enhance interleukin-8 (IL-8) production  
1833 (Balogh et al., 2019).

1834 Growing research is revealing the central role of Tregs at the maternal-fetal interface  
1835 during pregnancy in mammals (Teles et al., 2013; Wienke et al., 2019). Tregs play a central role  
1836 in immunosuppression in mammals (Attias, Al-Aubodah, & Piccirillo, 2019). Differentiation of  
1837 Tregs is governed by the transcription factor, *FOXP3* (Ramsdell & Rudensky, 2020).

1838 Alloantigen-dependent, uterine T cell signaling, and immunocompetent embryonic cells and their  
1839 products facilitate enhanced regulatory phenotypes of immune cells overall (Ander et al., 2019).

1840 The T-cell dependent adaptive immune system of mammals is unique. This may have  
1841 prompted their intricate balance of Treg mediators of immunotolerance at the maternal-fetal  
1842 interface (Chaouat, 2016). Birds rely more heavily on B cells. In non-avian reptiles, T helper  
1843 cells are functional, but the presence and function of other T cell subsets is unclear (Zimmerman,  
1844 2020; Zimmerman, Vogel, & Bowden, 2010). The potential role of T cells and Tregs in  
1845 viviparous squamate gestation should not be discounted. Treg-like cells have been identified in a  
1846 pufferfish, *Tetraodon nigroviridis* (Wen et al., 2011), suggesting that Tregs may have an ancient  
1847 evolutionary history.

1848

#### 1849 *(8) Progesterone, cytokines, and maternal-fetal immune dynamics*

1850 In addition to the role of progesterone in uterine quiescence (embryonic retention) and  
1851 hepatic vitellogenesis (nutrient provisioning), it also plays a role in maternal-fetal immune  
1852 dynamics. In the uterus of pregnant mammals, progesterone concentrations are associated with  
1853 altered B cell immunoglobulin secretion, inhibition of NK-cell mediated cytotoxicity and the shift  
1854 from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) dominated immune responses

1855 (Druckmann & Druckmann, 2005). Progesterone is also associated with immunomodulatory  
1856 effects (Ortega Brown et al., 1990). During gestation in *Agkistrodon piscivorus*, a viviparous pit  
1857 viper, progesterone concentrations are associated with decreased complement performance  
1858 (Graham et al., 2011), a portion of the immune system that promotes inflammation, among other  
1859 immune functions.

1860 In humans, progesterone induced protein (PIBF) is transported by placental extravillous  
1861 trophoblasts to maternal lymphocytes causing the induction of interleukin-10 (IL-10) production,  
1862 contributing to the Th2 dominant responses (Szekeres-Bartho, Šučurović, & Mulac-Jeričević,  
1863 2018). IL-10 is a potent anti-inflammatory cytokine that is produced by multiple cell types  
1864 (Zimmerman, Bowden, & Vogel, 2014). It is associated with Th2 response, and it inhibits Th1  
1865 responses. The phenotype of uterine macrophages is affected by trophoblasts when they secrete  
1866 IL-10 and macrophage colony-stimulating factor (M-CSF) (Svensson-Arvelund et al., 2021). IL-  
1867 10 inhibits IFN- $\gamma$  and increases in response to infection in chickens (Giansanti, Giardi, & Botti,  
1868 2006; Rothwell et al. 2004). In the uterus of the oviparous skink, *Lampropholis guichenoti*,  
1869 during gravidity and non-gravidity, IL-10 is expressed (Griffith et al., 2016).

1870 Proinflammatory cytokines may be downregulated during reproductive periods to limit  
1871 maladaptive immune responses to the foreign fetus (Zimmerman, Vogel, & Bowden, 2010). In  
1872 mammals, IL-1 allows release of hormones in human trophoblasts (Petraglia et al., 1990;  
1873 Masuhiro et al., 1990; Yagel et al., 1989), facilitates implantation (Haimovici, Hill, & Anderson,  
1874 1991; Hill, 1992; Tartakovsky & Ben-Yair, 1991), and influences the initiation of labor (Romero  
1875 et al., 1989, 1992). Regulation of the proinflammatory cytokines tumor necrosis factor (TNF)  
1876 and interleukin 1B (IL-1 $\beta$ ) is of particular importance in eutherian pregnancy (Haider & Knöfler,  
1877 2009; Paulesu, Romagnoli, & Bigliardi, 2005; Saito et al., 2010; Tayade et al., 2006).

1878 The uterine tissue of two reproductively bimodal squamates—viviparous individuals of  
1879 *Chalcides chalcides*, and oviparous and viviparous individuals of *Zootoca vivipara*—express IL-  
1880  $1\beta$  (Paulesu et al., 1995, 2005; Romagnoli et al., 2003). In the uterus of the viviparous skink,  
1881 *Pseudemoia entrecasteauxii*, during gestation regulation of TNF and IL- $1\beta$  at the transcriptional  
1882 and post-translation levels, respectively, may reduce inflammation (Hendrawan et al., 2017). The  
1883 pro-inflammatory function of IL- $1\beta$  in *Pseudemoia entrecasteauxii* may play a role developing a  
1884 more complex placenta (Hendrawan et al., 2017). The placenta of *Chalcides chalcides* expresses  
1885 pro-inflammatory cytokines, IL- $1\alpha$  and IL- $1\beta$ , at specific times during gestation (Paulesu et al.,  
1886 1995). During gestation, *Chalcides ocellatus* also differentially expresses 27 other interleukins  
1887 and interleukin related products (Brandley et al., 2012).

1888 The expression of IL-34 in a marsupial, the fat-tailed dunnart, during pre-implantation  
1889 (Whittington et al., 2018) may have an immunosuppressive function to help tolerate potential  
1890 contact of maternal and fetal tissues when the embryonic shell coat disintegrates (Lindau et al.,  
1891 2015). In chickens, IL-34 regulates Th1 and Th17 cytokine production (Truong et al., 2018).  
1892 During gestation in *Pseudemoia entrecasteauxii*, IL-16 and IL- $1\alpha$  are expressed in addition to  
1893 three receptors for Th17 family cytokines—IL-17RA, IL-17RC, and IL-17RA (Griffith,  
1894 Brandley, et al., 2016, 2017). In the yolk sac of *Pseudemoia entrecasteauxii* during pregnancy  
1895 interleukin related molecules, *ILDR1*, *IRAK1*, and *SIGIRR*, are differentially expressed (Griffith  
1896 et al., 2016). This profile suggests the presence of tricellular tight junctions and/or tricellulin  
1897 (Higashi et al., 2013; Ikenouchi et al., 2005), and regulation of toll-like receptors (TLRs) and/or  
1898 IL-1R signaling (Kawagoe et al., 2008; Lin, Lo, & Wu, 2010; Muzio et al., 1997).

1899

1900 (9) *The major histocompatibility complex and maternal-fetal immune dynamics*

1901 A substantial amount of literature on maternal-fetal immune dynamics was focuses on uNK  
1902 cells. Uterine NK cells have a distinct phenotype and function from peripheral NK cells. They  
1903 have several activating receptors (Manaster & Mandelboim, 2010) but do not exert cytolytic  
1904 functions on embryonic trophoblasts that they are in contact with (King, Birkby, & Loke, 1989).  
1905 Allorecognition of embryonic placental cells by uNK cells is a key regulator of the maternal-fetal  
1906 immune mechanisms that support placentation in mammals (Moffett & Colucci, 2014). When  
1907 cells lose their ability to express any HLAs, uNK cells are shown to kill them (Hunt et al., 2005;  
1908 Ishitani et al., 2003; King, Allen et al., 2000).

1909 In humans, expression of the classical MHC class I (C-MHCI) molecule HLA-C, and  
1910 nonclassical MHC class I (NC-MHCI) molecules HLA-E, HLA-F and HLA-G on trophoblasts  
1911 inhibit uNK cell-mediated cytotoxicity (Hunt et al., 2003; King, Burrows et al., 2000). Differing  
1912 from this, mismatched HLA-C profiles trigger rejection of the transplanted organs (Petersdorf et  
1913 al., 2014). Selection for balanced polymorphisms in HLA-C alleles and their killer  
1914 immunoglobulin receptors (KIRs) is proposed to be driven by reproductive success, rather than  
1915 immune recognition of pathogens (Trowsdale & Betz, 2006). Dimorphisms of HLA-C emerged  
1916 recently within primates (Adams & Parham, 2001).

1917 Similar patterns in MHC profiles have been explored in other viviparous amniotes. C-MHCI  
1918 antigen, H2-K, is expressed on giant trophoblast cells of mice and this is attributed to  
1919 trophoblast-induced uterine vasculature transformation (Arcellana-Panlilio & Schultz, 1994;  
1920 Chatterjee-Hasrouni & Lala, 1982; Hedley et al., 1989; King et al., 1987; Sellens, Jenkinson, &  
1921 Billington, 1978). H2-D antigen is co-expressed with H2-K in virtually all their other nucleated  
1922 cells (Madeja et al., 2011). However, H2-K expressing trophoblasts lack H2-D expression. This



1923 parallels the expression patterns of C-MHC molecules at the maternal-fetal interface in humans  
1924 and may be an evolutionarily conserved pattern (Madeja et al., 2011).

1925 In humans, NC-MHCI molecule, HLA-G, is especially tolerogenic (Carosella et al., 2015;  
1926 González et al., 2012; Hviid et al., 2004; Kovats et al., 1990). In adults, HLA-G is almost  
1927 exclusively expressed by fetal trophoblasts compared to adult cells (Faulk & Temple, 1976;  
1928 King, Burrows et al., 2000; Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al.,  
1929 1997). It supports immunotolerance at the maternal-fetal interface (Rebmann et al., 2014). The  
1930 role of HLA-G in supporting tolerogenic responses to organ transplants appears to be an  
1931 exploitation of its role in immunotolerance in the utero during pregnancy (Rebmann et al., 2014).  
1932 HLA-G is upregulated by several molecules that serve essential roles during gestation including  
1933 progesterone (Yie, Xiao, & Librach, 2006; Yie et al., 2006), IFN- $\alpha$ , IFN- $\beta$ , and IFN- $\gamma$  (Rebmann  
1934 et al. 2003; Lefebvre et al., 2001; Ugurel et al., 2001; Yang, Geraghty, & Hunt, 1995), and IL-10  
1935 and TGF- $\beta$  (Cadet et al., 1995; Moreau et al., 1999).

1936 A similar NC-MHCI gene to HLA-G exists in horses (Davies et al., 2006) where it likely  
1937 functions to protect the embryo from NK-cell mediated attack (Ott et al., 2014). NC-MHC  
1938 molecules with similar structure to HLA-G are also found in Rhesus monkeys (Boyson et al.,  
1939 1997) and baboons (Stern et al. 1987). Mice have two NC-MHCI genes that are expressed on the  
1940 surface of their placentas and on pre-implanted embryos (Sipes et al., 1996).

1941 In the gestating uterus of the viviparous skink, *Pseudemoia entrecasteauxii*, four putative C-  
1942 MHCI and two putative NC-MHCI molecules are expressed (Murphy, Thompson, & Belov,  
1943 2009). This pattern resembles the C-MHCI and NC-MHCI expression profiles of mammals,  
1944 suggesting that this viviparous skink utilizes a similar physiological mechanism to 'hide' the  
1945 embryo (Murphy, Thompson, & Belov, 2009). One of the putative NC-MHCI genes (Psen-

1946 160Ut/Psen-78G) has a substitution at position 150 where a tryptophan is substituted for a  
1947 leucine (Murphy, Thompson, & Belov, 2009). When Psen-160Ut/Psen-78G was aligned to NC-  
1948 MHC I genes of vertebrates ranging from fish to eutherian mammals, tryptophan was conserved  
1949 at position 150 except in Psen-160Ut/Psen-78G and HLA-G (Murphy, Thompson, & Belov,  
1950 2009). Whether this reflects an evolutionary history associated with immune tolerance at the  
1951 maternal-fetal interface in *Pseudemoia entrecasteauxii* requires further investigation.

1952 MHC I genes are also expressed in reproductive tissues of oviparous skinks (*Ctenotus*  
1953 *taeniolatus* and *Lampropholis guichenoti*) during non-reproductive periods and during late  
1954 gravidity (Murphy, Thompson, & Belov, 2009). A similar pattern is found in viviparous skinks  
1955 *Eulamprus tympanum*, *Niveoscincus metallicus*, *Pseudemoia entrecasteauxii* and the  
1956 reproductively bimodal skink *Saiphos equalis* which all express MHC I genes at non-  
1957 reproductive periods and during late pregnancy/gravidity (Murphy, Thompson, & Belov, 2009).  
1958 MHC gene H2-EA is also expressed during gestation with long egg retention in *Saiphos equalis*.

1959 The butyrophilin subfamily 1 member A (*BTN1A1*) is located in the MHC I region of the  
1960 genome in mammals (Trowsdale, 2011). *BTN1A1* is differentially expressed in the uterus during  
1961 gestation in a viviparous lizard, *Chalcides ocellatus* (Brandley et al., 2012). *BTN1A1* may have  
1962 important antimicrobial properties in chicken eggshells (Mann, Maček, & Olsen, 2006). In  
1963 mammals *BTN1A1* is the major protein associated with fat droplets in milk (Jeong et al., 2009).

1964

1965 (10) *Microchimerism and maternal-fetal immune dynamics*

1966 Billingham, Brent and Medawar suggested the concept of actively acquired immunologic  
1967 tolerance during pregnancy 70 years ago (Billingham, Brent, & Medawar, 1953; Ribatti, 2015).  
1968 Subsequent research over the following decades revealed that substantial transfer of proteins,

1969 parasites and even immunologically active cells occurs between mother and embryo (Adams &  
1970 Nelson, 2004; Axiak-Bechtel et al., 2013; Bakkour et al., 2014; Burlingham, 2010; Fujiki et al.,  
1971 2008; Gitlin et al., 1965; Khosrotehrani et al., 2005; Owen, 1945; Turin et al., 2007).  
1972 Microchimerism, where there is <0.1% donor chimeras in host tissue, is relatively pervasive  
1973 among eutherians during pregnancy. It plays a role in establishing tolerance to non-inherited  
1974 antigens. For example, cell populations from the mother that are transferred into embryonic  
1975 lymph nodes enable the establishment of embryonic Tregs that are tolerogenic toward non-  
1976 inherited maternal antigens (Mold et al., 2008).

1977       Microchimeric cellular populations are transferred across all placental types (Axiak-Bechtel  
1978 et al., 2013; Bakkour et al., 2014; Fujiki et al., 2008; Khosrotehrani et al., 2005; Turin et al.,  
1979 2007). Fetal and maternal cells persist for decades after birth across a range of tissues in mother  
1980 and offspring, respectively (Adams & Nelson, 2004; Bakkour et al., 2014; Bayes-Genis et al.,  
1981 2005; Bianchi et al., 1996; Evans et al., 1999; Jonsson et al., 2008; Stevens et al., 2004). There is  
1982 even a call in the immunology literature to shift from the conventional paradigm of “self vs  
1983 other” to instead consider the “self” as inherently chimeric (Nelson, 2012). Given that  
1984 epitheliochorial placentation is sufficient to illicit microchimeric cell populations, the occurrence  
1985 of similar bidirectional cellular traffic is a reasonable possibility in viviparous squamates.

1986

1987       (11)       *Paternal alloantigens*

1988       Under tenants gleaned from transplant medicine, the maternal immune system would illicit  
1989 an attack response as early as insemination when maternal tissues are exposed to paternal  
1990 alloantigens (Borziak et al., 2016; Schumacher & Zenclussen, 2015; Seavey & Mosmann, 2006).  
1991 Instead, maternal cells immunologically recognize them at this time without attack (Schumacher

1992 & Zenclussen, 2015; Seavey & Mosmann, 2006; Zenclussen et al., 2010). Treg expansion, a  
1993 process with major influence on maternal-fetal immunotolerance in mammals, is proposed to be  
1994 driven by several different factors found in seminal plasma (Baratelli et al., 2005; Teles et al.,  
1995 2013). Mothers may maintain fetal-specific Tregs with memory of the paternal alloantigens  
1996 (Zenclussen et al., 2010), expediting Treg response in future pregnancies with the same father  
1997 (Rowe et al., 2012).

1998 Alloantigen exposure at the time of insemination is not restricted to mammals. Seminal fluid  
1999 of chickens contains two MHC I paternal alloantigens and one MHC II alloantigen (Borziak et  
2000 al., 2016). It also contains proteins involved in immunity and antimicrobial defenses (Borziak et  
2001 al., 2016). In hens, evidence suggests that a protective local immunity to pathogens is established  
2002 after exposure to semen but the mechanisms for this remain unclear (Reiber & Conner, 1995;  
2003 Reiber, Conner, & Bilgili, 1995).

2004 In mammals, paternal alloantigens and cytokines in seminal fluid drive immune tolerance  
2005 (Schjenken & Robertson, 2014). Mammalian seminal plasma contains immune-factors (Kelly,  
2006 1995; Schjenken & Robertson, 2014)—TGF- $\beta$  (Breuss et al., 1993; Chu & Kawinski, 1998;  
2007 Slater & Murphy, 1999), IL-8 (Gutsche et al., 2003), and soluble IL-2 receptor (Srivastava,  
2008 Lippes, & Srivastava, 1996), prostaglandin E2 (PGE2) and 19-hydroxyprostaglandin E (19-  
2009 hydroxy PGE) (Denison et al., 1999), soluble tumor necrosis factor (TNF) receptors (Liabakk et  
2010 al., 1993), receptors for the Fc portion of  $\gamma$ -globulin, spermine (Evans, Lee, & Flugelman, 1995),  
2011 and complement inhibitors (Kelly, 1995). In horses and pigs, respectively, the proteins CRISP3  
2012 (Doty et al., 2011), PSP-I and PSP-II (Rodriguez-Martinez et al., 2010), act as signaling agents  
2013 in seminal fluid.

2014 Secretions of growth factors, cytokines and chemokines from cervical and endometrial  
2015 tissues immediately following insemination generates a proinflammatory environment that likely  
2016 aids in implantation. In the utero-vaginal junction of chickens and the utero-tubal junction of  
2017 pigs, expression of several genes were shared following mating compared to non-mating and  
2018 these genes were involved with immune-modulation (*IFIT5*, *IFI16*, *MMP27*, *ADAMTS3*, *MMP3*,  
2019 *MMP12*) and pH-regulation (*SLC16A2*, *SLC4A9*, *SLC13A1*, *SLC35F1*, *ATP8B3*, *ATP13A3*), a  
2020 process essential for implantation (Atikuzzaman et al., 2017, 2015). Instead of mounting an  
2021 attack, it appears that the uterine immune system and paternal genes work cooperatively to  
2022 support pregnancy in mammals and gravidity in birds. Whether this applies to reptiles, and how  
2023 it may influence immune dynamics involved with squamate parity mode evolution, deserves  
2024 investigation.

2025

2026 (12) *Discussion and future directions—maternal-fetal immune dynamics & the*  
2027 *evolution of parity modes*

2028 Immune processes appear to be important for both oviparity and viviparity—as evidenced  
2029 here, in part, by overlapping expression profiles of immune genes in female reproductive tissues  
2030 of chickens and pigs, expression of paternal antigens in avian seminal fluid, and uterine  
2031 expression of maternal antigens in oviparous and viviparous skinks. This highlights the scientific  
2032 advances made since Medawar’s paradigm, when embryos were treated as analogs to allografts.  
2033 Nonetheless, viviparity is associated with complex immune dynamics between maternal, fetal,  
2034 and paternal tissues.

2035 Overall, evolving appropriate immunological responses is one hurdle of transitions to  
2036 viviparity in squamates. This is evidenced by the unique MHC expression profiles identified in

2037 some viviparous skinks compared to oviparous relatives (Murphy et al., 2009); and the detection  
2038 of divergent selection in immune response genes in viviparous and oviparous *Zootoca vivipara*  
2039 (Recknagel et al., 2021a). Labile parity modes in squamates may be supported if they are more  
2040 heavily reliant on the innate immune system for reproduction. However, reptiles may not have  
2041 distinguished innate and adaptive immune systems (Zimmerman et al., 2020).

2042 Changes to genes that serve overlapping functions across the Main Five may have a  
2043 disproportionate influence on transitions between parity modes. In this section I reviewed two  
2044 molecules, *TGF-β* and progesterone, that exert influence on multiple Main Five categories.  
2045 Progesterone influences uterine quiescence (embryonic retention), hepatic vitellogenesis  
2046 (nutrient provisioning) and regulation of inflammatory responses in utero (maternal-fetal  
2047 immune dynamics). Genes in the *TGF-β* family play a role in placental development and  
2048 maternal-fetal immune dynamics. *TGF-β* family is implicated in placental development in  
2049 eutherians (Hempstock et al., 2004; Caniggia et al., 2000; Lafontaine et al., 2011). A *TGF-β*  
2050 receptor protein (*TGFBR1*) was associated with placental development in *Phrynocephalus*  
2051 *vlangalii* (Gao et al., 2019). In humans *TGF-β* upregulates tolerogenic HLA-G in utero and is an  
2052 immune factor in mammalian seminal fluid. Multiple genes in the *TGF-β* family are also  
2053 differentially expressed during gestation in other viviparous lizards, *Pseudemoia entrecasteauxii*  
2054 and *Saiphos equalis* (Foster et al., 2020; Griffith et al., 2016). Examining the functions of *TGF-β*  
2055 and progesterone across other amniotes may reveal insights into how these molecules influence  
2056 the evolution of parity modes.

2057 In mammals, inflammation appears to be involved with two of the Main Five processes—  
2058 regulation of maternal-fetal immune dynamics and embryonic retention. It is intriguing to  
2059 consider the implications this has for the interconnectedness of the Main Five. Greater

2060 interconnectedness would suggest that changes to few genes involved with the Main Five could  
2061 cause a cascading effect to support more labile transitions between parity modes.

2062       Implantation and parturition in therian mammals evolved from a shared inflammatory  
2063 attachment reaction (Hansen et al., 2017). The process of implantation has important  
2064 implications for maternal-fetal exchanges of inorganic and organic material and maternal-fetal  
2065 immune dynamics. Given that inflammation is associated with implantation and parturition  
2066 implicates it in gas, water, and nutrient provisioning (including calcium here), maternal-fetal  
2067 immune dynamics and length of embryonic retention. However, implantation in mammals and  
2068 viviparous squamates is not homologous (Griffith, Van Dyke, & Thompson, 2013). Therefore, it  
2069 is difficult to make inferences about how substantial the influence of inflammation is on the  
2070 evolution of parity modes in squamates. Nonetheless, the abundant literature on uterine  
2071 inflammatory processes during human pregnancy and the evolution of inflammatory processes  
2072 that supported the evolution of viviparity in mammals (Challis et al., 2009; Chavan, Griffith, &  
2073 Wagner, 2017; Mor et al., 2011; Griffith, Chavan et al., 2017; Stadtmauer & Wagner, 2020a)  
2074 serve as indispensable resources for exploring the role of inflammation in squamate viviparity. I  
2075 resist expanding on this further. I suspect that the immune system plays a central role in dictating  
2076 the plasticity of parity modes. However, further work is necessary to validate this.

2077

2078

## 2079       **VII. Conclusions**

2080

2081       (1) Through holistic consideration of the unique complexity of parity mode evolution, within  
2082       the context of genomic and transcriptomic studies across interdisciplinary fields, this

2083 review provided a new perspective on the history of parity mode transitions in amniotes  
2084 and squamates. The overlapping activity of immune genes in utero, genes for calcium  
2085 transport, placentation, and hormonal regulation across mammals, birds, and reptiles hint  
2086 at discoveries to be made. There is a fascinating history to the evolutionary physiology  
2087 and genomics of reproduction in amniotes that is ripe for downstream research.

2088 (2) Changes to gene(s) or physiological processes associated with more than one of the Main  
2089 Five should disproportionately influence parity mode evolution—*SLC* gene superfamily,  
2090 TGF- $\beta$ , *BMPRI*B, progesterone, *PMCA*, calbindin-D28K, *SPP1*, sustained functioning of  
2091 the corpora lutea and inflammation, and the genes associated with both gestation length  
2092 and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).

2093 (3) Growing evidence in the medical literature suggests that immune system interactions at  
2094 the maternal-fetal interface in mammals did not evolve simply through tolerance,  
2095 evasion, or suppression (Chaouat, 2016; Chavan, Griffith, & Wagner, 2017; Moffett &  
2096 Loke, 2004, 2006). Instead, maternal-fetal immune dynamics have a deep evolutionary  
2097 history that enables both embryo and mother interact cooperatively (Yoshizawa, 2016).  
2098 Future research on amniote parity mode evolution should consider maternal-fetal immune  
2099 dynamics in this context. Nonetheless, viviparity and extended embryonic retention are  
2100 assuredly associated with immunological responses in squamates (e.g. Foster et al.,  
2101 2020).

2102 (4) Compared to viviparous endothermic amniotes, ectothermy likely influences parity mode  
2103 evolution differently because it entails slower antibody responses and a greater reliance  
2104 on climatic conditions for embryonic development. This and the Cold Climate  
2105 Hypothesis are likely relevant to the origin of the amniotic egg and squamate parity mode



2106 evolution. Climatic shifts during the origin of amniotes should be explored for their  
2107 consistency with the EER model.

2108 (5) Two new mechanisms for transitions between oviparity and viviparity, without  
2109 necessitating intermediate stages, stand out from the cumulative research on the Main  
2110 Five. These are presented here (Conclusions 6 and 7) as tools to be broadened and  
2111 challenged with the goal of advancing scientific insight on the subject.

2112 (6) The genomics and physiology of amniote parity mode evolution does not preclude an  
2113 origin of viviparity in the MRCA of Lepidosauria. I propose the following mechanism—a  
2114 change to the phenotype or function of mammillary knobs occurred in the MRCA of  
2115 Lepidosauria, instantaneously preventing calcium carbonate deposition (basal cap  
2116 hypothesis); the eggshell loss enabled uterine exposure to chorioallantoic progesterone  
2117 production (extending embryonic retention) and incipient calcium matrotrophy  
2118 (supporting embryonic development); parturition occurred via 1) placental progesterone  
2119 withdrawal or 2) overdistension of the uterus triggers contractions. This is one way to  
2120 imagine viviparity evolving in the MRCA of Lepidosauria.

2121 a. Hypothesis testing: If the genes that code for the KS-proteoglycan, “mammillan”,  
2122 that makes up mammillary knobs are absent or non-functional across squamates  
2123 and tuatara, then this would support the basal cap hypothesis. To test this  
2124 hypothesis, the genes must be identified in Archelosaur genomes and proteomes.  
2125 Additionally, ancestral state reconstructions on the eggshell and eggshell  
2126 membrane should be generated across oviparous and viviparous Archelosaurs,  
2127 utilizing current recommendations for characterizing eggshell microstructure

2128 (Legendre et al., 2022). This will require also developing a system to accurately  
2129 characterize eggshell membranes.

2130 (7) As discussed, the calcium secreting capacity of the uterus is maintained in oviparous  
2131 viviparous squamates. Nonetheless, a reversal back to oviparity may evolve most easily  
2132 within viviparous clades with matrotrophic calcium provisioning through the following  
2133 sequence of events—calcium secretions in utero stick to the eggshell membrane instead  
2134 of being absorbed by the chorioallantois; oviposition can then occur early in embryonic  
2135 development in one of two ways 1) the death of corpora lutea or 2) the calcified eggshell  
2136 blocks a threshold of chorioallantoic progesterone production from reaching uterine  
2137 tissue; the calcified eggshell provides embryonic calcium that is transported upon  
2138 embryonic metabolic demand.

2139 a. Hypothesis testing: Recent reversals should have physiological or genomic  
2140 remnants of a viviparous past. Given that viviparous squamates generally have  
2141 more active uterine immune systems to support gestation, oviparous reversals  
2142 should 1) have more immune genes expressed in utero than ancestrally oviparous  
2143 squamates, and 2) these immune genes should have stronger signatures of relaxed  
2144 selection than immune genes expressed in a close relative during viviparous  
2145 gestation.

2146  
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2153       **IX.   References**

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